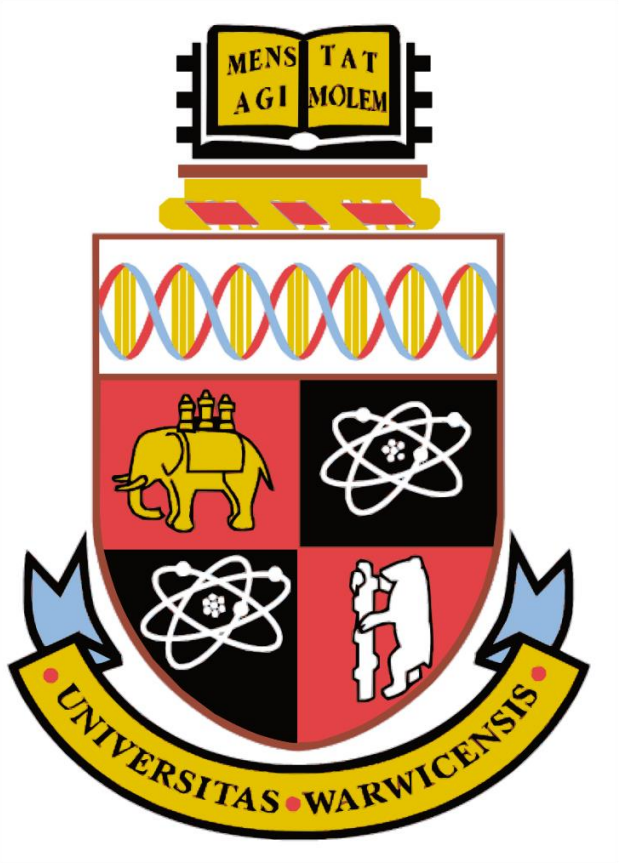
The Controlled Radical Polymerisation of Hydrophobic and Cationic Monomers *via* Cu(0)-RDRP



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A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy in Chemistry

Department of Chemistry, University of Warwick

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This thesis is dedicated to the memory of my father who I miss every day, and to my mother who through the tough times has been a constant source of love, support and encouragement.

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Abbreviations

AA	Acrylic acid
AGET	Activators generated by electron transfer
AIBN	Azobisisobutyronitrile
ARGET	Activators regenerated by electron transfer
ATRP	Atom transfer radical polymerisation
BA	Butyl acrylate
BHT	Butylated hydroxytoluene
BPN	2-bromopropiontrile
BPY	Bipyridine
CCTP	Catalytic chain transfer polymerisation
CTA	Chain transfer agent
Cyclam	1, 4, 8, 11-tetraazacyclotetradecane
DCTB	Trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propyldene] malonitrile
DMAEA	Dimethylaminoethyl acrylate
DMAEMA	Dimethylaminoethyl methacrylate
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DP	Degree of polymerisation
DRI	Differential refractive index
dsRNA	double stranded RNA
eATRP	Electrochemical atom transfer radical polymerisation
EBiB	Ethyl-α-bromoisobutyrate
EBP	Ethyl-2-bromopropionate
FRP	Free radical polymerisation
HCl	Hydrochloric acid
HEBiB	Hydroxyethyl-α-bromoisobutyrate
HMTETA	1, 1, 4, 7, 10, 10-hexamethyltriethylenetetramine

HPLC	High performance liquid chromatography
ICAR	Initiators for continuous activator regeneration
IPA	Isopropanol
IUPAC	International Union of Pure and Applied Chemistry
LRP	Living radical polymerisation
LS	Light scattering
MALDI	Matrix assisted laser desorption ionisation
MeCN	Acetonitrile
$[M]_0$	Concentration of monomer at time zero
$[M]_t$	Concentration of monomer at time t
MA	Methyl acrylate
MBP	Methyl-2-bromopropionate
MD	Molecular dynamics
Me_6Tren	Tris[2-(dimethylamino)ethyl]amine
MMA	Methyl methacrylate
MWD	Molecular weight distribution
MWt	Molecular weight
NMP	Nitroxide mediated polymerisation
NMR	Nuclear magnetic resonance
M_n	Number average molecular weight
M_w	Weight average molecular weight
PAA	Poly(acrylic acid)
PBMA	Poly(butyl methacrylate)
PBS	Phosphate buffer solution
PDMAEA	Poly(dimethylaminoethyl acrylate)
PDMAEMA	Poly(dimethylaminoethyl methacrylate)
PEGMA	Poly(ethylene glycol methyl ether methacrylate)
PEMA	Poly(ethyl methacrylate)
PMA	Poly(methyl acrylate)
PMDETA	*N,N,N′,N″,N‴*-pentamethyldiethylenetriamine

PMMA	Poly(methyl methacrylate)
PNIPAm	Poly(N-isopropyl acrylamide
PRE	Persistent radical effect
PS	Polystyrene
PTFE	Poly(tetrafluoroethylene)
RAFT	Reversible addition fragmentation chain transfer
RDRP	Reversible deactivation radical polymerisation
RNA	Ribonucleic acid
RNAi	RNA interference
RNAses	Ribonucleases
SARA	Supplemental activator and reducing agent
SEC	Size exclusion chromatography
SET LRP	Single electron transfer living radical polymerisation
STY	Styrene
tBuOH	Tert-butanol
TEA	Triethylamine
TEMPO	2,2,6,6,-tetramethylpiperidinyl-1-oxy
TFE	Trifluoroethanol
TFP	Tetrafluoropropanol
THF	Tetrahydrofuran
ToF	Time of flight
TMEDA	Tetramethylethylenediamine
TPMA	Tris(2-pyridylmethyl)amine
TREN	Tris(2-aminoethyl)amine
VS	Viscometry

Acknowledgments

First of all, I would like to thank Professor David Haddleton for allowing me to undertake a PhD under his supervision. From the very first day to the last, Dave has been the best possible supervisor. He truly cares for his students, provides constant positivity and encouragement, and will answer any question, be it a scientific or life related. His willingness to explore every interesting result and attitude of "just do it" is infectious and has made completing research very enjoyable. I have so many fond memories that I will take away with me from my time in the Haddleton Group, and am thankful to Dave for all the great opportunities. Particularly I have to mention the time I spent at Syngenta and as a visiting scholar at UCSB, but there were some great conferences too.

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There are a number of people who have made a significant difference not only to my PhD but to my life in general. Firstly, I was very lucky to meet Dr. Athina Anastasaki and to subsequently collaborate with someone so motivated. Over time I have come to

appreciate nothing more than her directness and honesty. I can't count the number of times I thought a project was finished, and was then been told there were more experiments to do! But it always made the research so much better. I have never met anyone who cares more for the science they are doing, and who will spend any length of time enhancing the quality of the work and encouraging those around her to grow and improve.

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the early days, and also my current office members Yonguang Li, George Patias, Arkadios Marathianos, and Mohammed Aljuaid who are all very positive and friendly influences to be around on a day to day basis. I must also thank Paul Wilson (NMR and Football), Patrick de Jongh (Mt. Snowdon), Atty Shegiwal (many late evening sauna discussions and meals), Alan Wemyss (many scientific and political discussions), Joji Tanaka, Nuttapol Risangud (see you in Thailand) and both Sams (Lowe and Lawton). I have also been very lucky to share a house with some very good friends, in particular Sam Lawton and Nicholas Kuht with whom curry night and love life discussions have made Thursday evenings so enjoyable.

My final acknowledgement goes to Laura. For the last 4 years and longer you have always been there for me, you are my best friend and I am so lucky to spend so many lovely times with you. I hope in the future, we will live in the same place, and have many more great experiences together.

Declaration

Experimental work contained in this thesis is original research carried out by the author, unless otherwise stated, in the Department of Chemistry of the University of Warwick, between September 2014 and July 2018. No material contained herein has been submitted for any other degree, or at any other institution.

Results from other authors are referenced in the usual manner throughout the text.

- Gel electrophoresis assays and soil stability assays (chapter 5) were acquired at Syngenta (Jeallott's Hill International Research Centre, Berkshire, England).
- All atom molecular dynamics (chapter 5) were acquired by Dr. Tuan Nguyen (University of Queensland, Brisbane, Australia).

Date:

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Richard Whitfield

Abstract

Cu(0)-RDRP can utilise significantly lower catalyst loadings than conventional ATRP methodologies, yielding high conversions and low dispersities. This technique has a simple set-up with reactions typically carried out in glass vials and deoxygenation simply *via* a short period of nitrogen bubbling. The synthesis of polyacrylates and polyacrylamides has resulted in many successes with a wide scope of materials previously prepared, but the polymerisation of low k_p monomers, for example methacrylates and styrene has resulted in significant challenges. Polymerisation conditions that are successful for one monomer or monomer class typically fail for others, so there is no means of knowing the optimal conditions for carrying out a particular polymerisation. Therefore the selection of appropriate conditions for successful polymerisation can be a time consuming and arduous task for both "experts" and non-experts. In chapter 2 of this thesis, one set of conditions are optimised to yield well-defined polyacrylate, polymethacrylate and polystyrene homo and block copolymers. There are very limited reports of the polymerisation of styrene *via* Cu(0)-RDRP, so further optimisation of this synthesis is provided in Chapter 3, yielding higher molecular weights while maintaining both a high initiator efficiency and a narrow dispersity.

A further notable area of challenge within the polymer community is the controlled polymerisation of cationic monomers with reported protocols observing many side reactions and termination events. PDMAEA has many ideal properties making it a good candidate for RNA interference, so this polymer has many potential applications. Chapter 4 illustrates the optimisation of the synthesis of linear and star polymers of DMAEA and the ability of these materials to bind and subsequently release dsRNA in

both aqueous solution and in soil is subsequently investigated in chapter 5. This is part of an industrial project funded by Syngenta.

Chapter 1: An Introduction into Polymers and the Development of Controlled Radical Polymerisation

1.1. A Brief History of Polymers

Polymers are materials made by bonding together many identical small units called monomers. Their synthetic history dates back thousands of years, with the first example illustrated by the Aztecs in 1600 BC, where a latex was extracted from rubber trees and mixed with fluid extracted from grapes, yielding the first processed rubber. However it was not until the 1830s, when the next breakthrough was achieved by Charles Goodyear and Nathaniel Hayward who discovered that by mixing natural rubber with sulfur at high temperatures, a crosslinked material was generated, which had more desirable properties than those possessed by either of the starting materials.[1] Two centuries later this material is still used in the majority of the world's rubber tyres. The next major leap was not until the early 20th century when Leo Baekeland, a Belgian chemist who later became known as "the father of plastics", discovered that on heating a mixture of phenol and formaldehyde at the right pressure, an insoluble polymeric material was generated. This material was the first thermosetting plastic which was christened Bakelite and is commonly found as the basis for electrical insulators.[2]

Further developments were achieved by Michael Polanyi who discovered the structure of a polymer, by analysing cellulose *via* x-ray crystallography[3, 4] and Hermann Staudinger (Nobel Prize 1953) who developed the foundations of polymer theory, by proposing that monomer units covalently bond together.[5] This was in direct contradiction to the rest of chemistry who believed that polymers were aggregations of small molecules. This was to be the catalyst for significant polymer research and development over the subsequent decades. By adjusting the chemical structure of the monomer, a vast array of different synthetic materials have been designed and prepared, with appropriate physical and chemical properties for a diverse range of applications. Polymers are omnipresent in

society today, with the most common "every day" materials utilised ranging from nylon (clothing and ropes) to polystyrene (plastic cutlery, cups and hair combs), poly(vinyl chloride) (pipes, window panels and credit cards), polyethylene (packaging and bottles) and polypropylene (packaging and textiles). "Smart" materials have also been developed which have one unique property that allow a precise application to be fulfilled for example, Kevlar in bullet proof vests[6], Teflon in non-stick frying pans[7] and Lycra found in elastic clothing.[8, 9] There are numerous other applications but it is noteworthy that these materials are not only limited to hard or rigid structures, but also soft materials which can be used in biological applications, for example tissue engineering, drug delivery, therapeutics and diagnostics.[10-12]

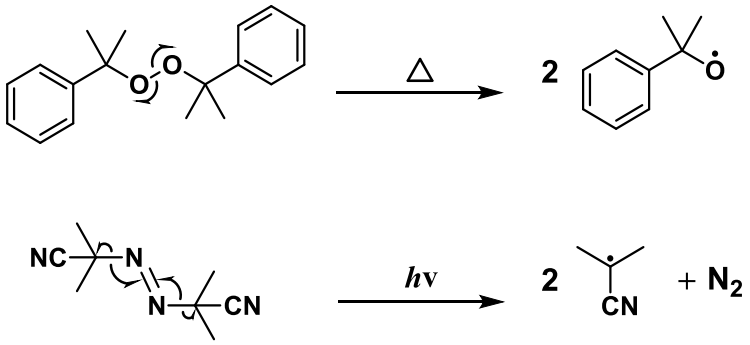
With this huge diversity in polymeric materials and vast array of applications, the methodologies of preparation are in constant evolution. This introduction will subsequently explore the development of free radical polymerisation (FRP), prior to the development of living polymerisation and RDRP (reversible deactivation radical polymerisation), before finally discussing the range of accessible polymeric materials and how to synthesise them.

1.2 Free Radical Polymerisation

Free Radical Polymerisation was first discovered by Staudinger in 1920, who made two very important breakthroughs. He was the first to suggest the involvement of a radical species, which he referred to as a trivalent carbon atom, and also proposed the concept of unstable chain ends which could grow until a time at which they became inactive.[5] This technique is the most well-known and most commonly used polymerisation procedure, with great versatility in terms of monomer scope and reaction conditions. Today, the relative simplicity and low cost of implementation means industrially FRP accounts for around 45% of all plastic materials produced and 40% of synthetic rubber. The mechanism of FRP is relatively simple, consisting of four steps: initiation, propagation, termination and chain transfer, which are explored in the subsequent sections.[13, 14]

1.2.1. Initiation

The first step of any FRP is the generation of a radical. This is achieved by the decomposition of an initiator molecule, typically utilising either heat (thermolysis), light (photolysis) or a redox reaction.[15] Common initiators are peroxy (first used by Fritz Klatte in 1912)[16] or azo compounds (first used by Schultz in 1939)[17], which on the application of one of these stimuli generate primary radicals, Scheme 1.1.[18] Please note that this reference to primary radicals refers to the first radicals formed during the polymerisation, rather than the sterics of the radicals formed.



Scheme 1.1: *The mechanism of initiation of a free radical polymerisation giving an example of thermolysis with dicumyl peroxide and photolysis with azobisisobutyronitrile (AIBN) in both cases illustrating the formation of primary radicals.*

These can then react with the carbon-carbon double bond of the monomer species, to give an initiating radical: the starting point of a polymer chain. Radicals by nature are extremely reactive, so therefore the rate of initiator degradation is significantly slower than the subsequent initiation and propagation steps.[14] Equation 1.1, illustrates that the initiator decomposition (k_d) is the rate determining step. Additionally a term f, which is known as the initiator efficiency is added to this equation, as not all of the primary radicals generated subsequently initiate polymer chains.[19] There is the potential for many side reactions, for example radical recombination, radical rearrangements and transfer to solvents, which result in termination of some of these primary radicals and reduced initiator efficiency.[14]

$$\boldsymbol{R_i = R_d = 2fk_d[I]} \qquad \textbf{(1.1)}$$

1.2.2. Propagation

The second step of a free radical process is propagation, the process by which the initiating radical sequentially reacts with monomer units, resulting in a rapidly growing polymer chain. There are two possible methods of propagation, namely head to head or head to tail addition. Head to tail is favoured as radical addition occurs to the least sterically hindered site. Propagation subsequently proceeds until either all monomer is

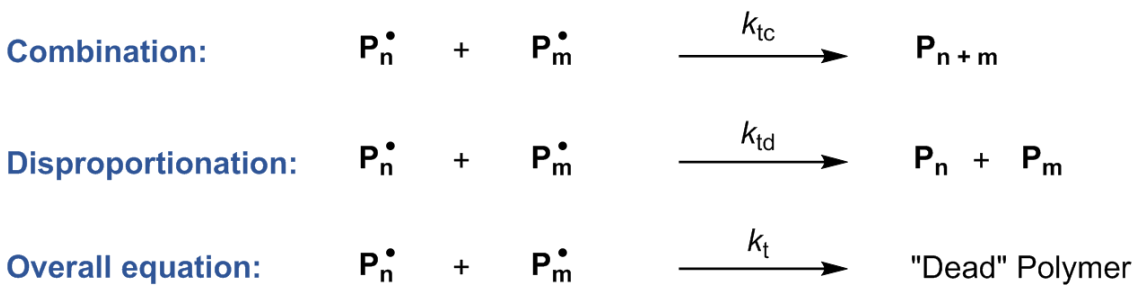
consumed or a termination event has occurred. The expression for the rate of propagation is therefore proportional to the concentration of monomer and propagating radicals (Equation 1.2).[13]

$$R_p = k_p[M][P\bullet] \qquad \textbf{(1.2)}$$

It is worthy of note, that conditions have to be carefully selected to avoid auto-acceleration during polymerisation. Auto-acceleration (or the Trommsdorff-Norrish effect) is a dangerous reaction, where polymerisation results in localised viscosity and the generation of heat. This results in a further increase in viscosity and temperature and a subsequent rapid increase in the overall rate of reaction. These runaway reactions in combination with a lack of heat dissipation can result in the destruction of the reaction vessel or explosion. [20]

1.2.3. Termination

Termination occurs when any propagating radical is irreversibly quenched, so can no longer react with monomer. This polymer chain is therefore commonly described as "dead". There are two main methods for bimolecular termination between polymer chains which are combination or disproportionation (Scheme 1.2).[21]



Scheme 1.2: Termination methods of termination of a free radical polymerisation, with combination and disproportionation illustrated.

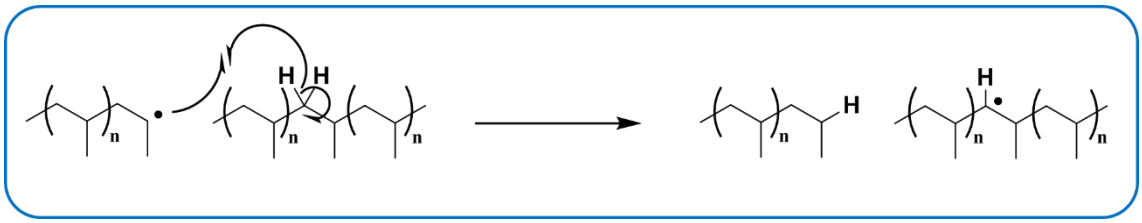
Combination is simply the result of the radical chain ends of two separate polymer chains reacting, forming one "dead" polymer chain consisting of the combined molecular

weight of both the original polymer chains. The rate of this reaction is therefore proportional to the concentration of propagating radicals ([P•]) (Equation 1.3). For the case of disproportionation, a chain end radical abstracts a proton from a neighbouring chain, yielding two "dead" polymer chains, one of which is capped by a proton and the other with a double bond. Both termination events rate constants (k_{tc} and k_{td}) are kinetically equivalent, and both have the same rate equation. These terms are therefore typically combined into one rate constant known as k_t.[22]

$$R_t = 2k_t[P\bullet]^2 \qquad (1.3)$$

1.2.4. Chain Transfer

The final factor to consider within free radical polymerisation is the very common side reaction called chain transfer.[23] This is a method of termination of a polymer chain, but results in the formation of a new radical, which then has the ability to propagate, so does not result in a change in the overall number of radicals in the system. Chain transfer can occur with solvent, initiator or monomer, resulting in a lower average molecular weight within the polymerisation mixture, or to polymer which can result in branching and higher molecular weights, Scheme 1.3.



Scheme 1.3: Reaction mechanism of chain transfer occurring between polypropylene chains.

Catalytic chain transfer polymerisation (CCTP) has been developed as a technique, where low spin cobalt(II) complexes are utilised as chain transfer agents (CTAs) so to generate low molecular weight polymers. The effectiveness of a CTA is

determined by its chain transfer constant (C_s), which is a ratio of rate of chain transfer (k_{tr}) compared to the rate of propagation (k_p) (Equation 1.4).[24, 25]

$$C_s = \frac{k_{tr}}{k_p} \quad \textbf{(1.4)}$$

Experimentally, the chain transfer constant can be calculated using the Mayo equation, by utilising the ratio of the degree of polymerisation in the presence (DP_n) and absence (DP_{n0}) of CTA ([CTA] and [M] are the concentrations of CTA and monomer respectively, Equation 1.5).

$$\frac{1}{DP_n} = \frac{1}{DP_{n0}} + C_s \frac{[CTA]}{[M]} \quad \textbf{(1.5)}$$

1.2.5. Kinetics of Free Radical Polymerisation

It is quite complex to understand the overall rate of a free radical polymerisation, as the rate of polymerisation is proportional to the concentration of radicals. Radical lifetime is so short, and the concentration is constantly evolving, so measuring the number of propagating radicals is a significant hurdle. Therefore a number of assumptions have been applied to the system. A steady state assumption is used, in which the rate of radical formation and destruction are considered equal thus the radical concentration remains constant throughout the polymerisation. This isn't accurate though for a free radical polymerisation, as the rate of radical generation and termination will vary during different stages (i.e. decomposition of the initiator). Other assumptions include that initiator dissociation is the rate determining step, initiation results in no monomer consumption and the rate of propagation and termination are independent of chain length. Utilising these steady state approximations, the concentration of propagating radicals can be calculated by rearranging the expression for the rate of termination (Equation 1.6). This along with the equation for the rate of initiation (Equation 1.7) can then be substituted

into the rate equation, yielding the overall rate of free radical polymerisation (Equation 1.8).[13] Detailed derivations of kinetics are illustrated in the equations below.

$$R_i = R_t = 2k_t[P\bullet]^2 \quad \textbf{(1.6)}$$

$$R_p = k_p[M][P\bullet] = k_p[M]\sqrt{\left(\frac{R_i}{2k_t}\right)} \quad \textbf{(1.7)}$$

$$R_p = k_p[M]\sqrt{\left(\frac{fk_d[I]}{k_t}\right)} \quad \textbf{(1.8)}$$

1.2.6. Advantages and Limitations of Free Radical Polymerisation

The simplicity of the free radical polymerisation reaction set-up, the mild nature of conditions and the tolerance of procedures to impurities and trace amounts of oxygen allows the polymer chemist accessibility to a broad range of materials.[13] Successful scalability has been illustrated with billions of kilograms of polymers produced *via* this method each year. There are, however, potential limitations with FRP as these processes can yield unpredictable molecular weights and a broad distribution of chain lengths (dispersity typically around 2). This is due to the high radical concentration resulting in significant termination and chain transfer events. Further to this, it is particularly challenging to make complex macromolecular architectures, for example stars or block copolymers with this methodology due to the lack of an end group during polymerisation.[14, 23] A number of living polymerisation methodologies have therefore been developed to overcome these issues (Section 1.3).

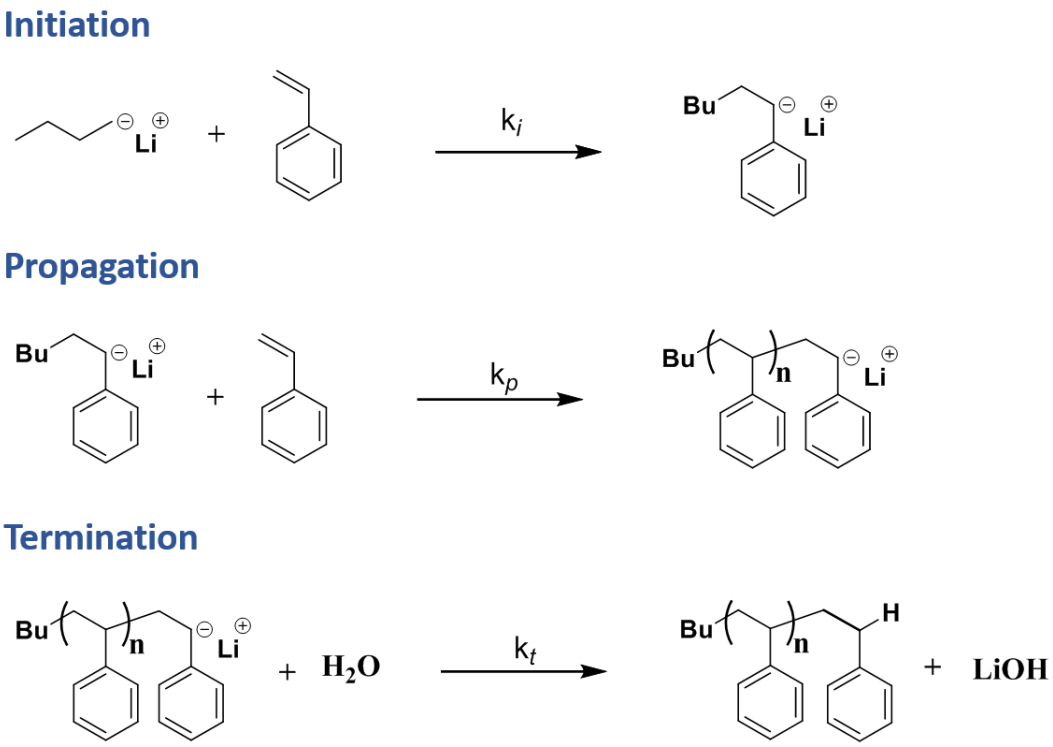
1.3. Living Polymerisation

The concept of a living polymerisation was first reported by Michael Szwarc in 1956.[26] In theory a "living" polymerisation has an absence of termination or chain transfer events, so all polymer chains grow at the same rate with low dispersity maintained

(typically less than 1.20). Molecular weight increases linearly with conversion until full conversion is achieved and the chain ends maintain their activity allowing for the addition of a second monomer and the synthesis of well-defined block copolymers. The synthesis of well-defined block copolymers has therefore become the norm with these techniques.

1.3.1. Living Anionic Polymerisation

Living anionic polymerisation was the first technique to provide polymer chemists with access to complex architectures and controlled molecular weights (Scheme 1.4).[27]



Scheme 1.4: The mechanism of living anionic polymerisation, with initiation by n-butyl lithium, propagation of styrene and termination via the reaction between the propagating anion and water illustrated.

This technique utilises reactive anions, such as *n*-butyl lithium or sodium napthalenide as the initiator.[28, 29] The combination of a rate of initiation much faster than propagation and the virtual absence of termination events, results in all chains starting at the same time and growing at the same rate, yielding well defined polymers with low dispersities. Molecular weights are close to theoretical values as determined by the degree

of polymerisation being equal to the concentration of monomer divided by the concentration of initiator (initiator efficiency 100%).[30]

There are however challenges associated with this technique, including limited monomer scope (predominantly styrene, isoprene and butadiene – hydrocarbons containing no heteroatoms) and the stringent conditions (anhydrous and oxygen free) required for successful polymerisation. The initiators and propagating chains are strongly nucleophilic so highly reactive with moisture, oxygen or any other protic species, so rigorous removal and purification of all reagents and solvents is required prior to polymerisation.[30] Despite these potential drawbacks, living anionic polymerisation has been successfully applied to synthesis on an industrial scale.[31]

1.3.2. Kinetics of Living Radical Polymerisation

There are a number of assumptions made for kinetic analysis of a living radical polymerisation (LRP). Firstly, during polymerisation there is an absence of chain transfer and termination events, so therefore a constant concentration of radicals throughout the polymerisation, resulting in a constant rate of propagation. It is also assumed that initiation is so fast that it is completed at time zero, so the rate equation can be simplified just to include the rate of monomer consumption over time (Equation 1.9). Therefore a plot of $\ln([M_0]/[M_t])$ against time should be linear if a living radical polymerisation has been achieved (Equation 1.10).[14]

$$\boldsymbol{R_p = \frac{-d[M]}{dt} = k_p[M][P\cdot]} \qquad \textbf{(1.9)}$$

$$\boldsymbol{ln\left(\frac{[M]_0}{[M]_t}\right) = k_p[P\cdot]t} \qquad \textbf{(1.10)}$$

This is one of seven tests for livingness, with a previous report by Quirk and Lee[32] illustrating more detailed requirements. For a reaction to be classified as "living" there

must also be a linear evolution of the number average molecular weight with respect to conversion, a linear reduction in dispersity with increasing conversion (in accordance with $Đ = 1 + 1/DP$) and the number of polymer molecules (and also active centres) must be constant. Reactions must proceed to quantitative yields (when all monomer has been consumed), and chain end functionality must be preserved so that on addition of a further aliquot of monomer the reaction will continue. Finally the molecular weight must be controlled by the stoichiometry of the reaction.

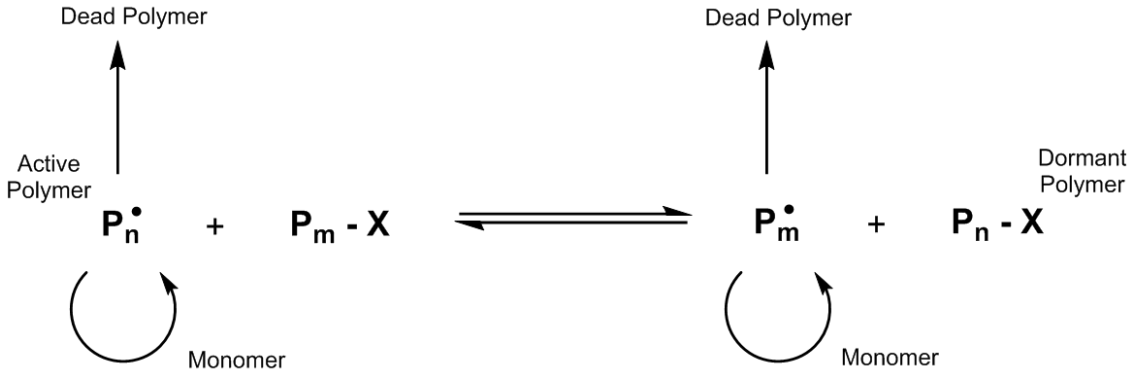
1.4 Reversible Deactivation Radical Polymerisation

In a similar manner to a living anionic polymerisation for a living radical polymerisation to occur there must be a total absence of termination or chain transfer events. However, due to the nature and reactivity of radicals, no polymerisation methodology can completely prevent these termination events. IUPAC (International Union of Pure and Applied Chemistry) has therefore modified its terminology to describe these methodologies from living radical polymerisation to reversible deactivation radical polymerisation or RDRP.[27]

The advent of reversible deactivation radical polymerisation techniques has opened new avenues for the synthesis of advanced materials that exhibit narrow molecular weight distributions (MWDs), high end group fidelity and precisely controlled molecular weight and architecture. The three common methodologies are reversible addition fragmentation chain-transfer polymerisation (RAFT)[33], nitroxide-mediated polymerisation (NMP)[34] and atom transfer radical polymerisation (ATRP)[35, 36], which will all be discussed in sections 1.4.1, 1.4.2 and 1.4.3 respectively. These techniques all incorporate a fast and reversible activation and deactivation between an active and a dormant state. Due to the high reactivity of radicals these equilibria must be predominantly in the dormant state so the overall concentration of active radicals is reduced. This allows all polymer chains to propagate at a consistent rate and prevents unwanted termination and side reactions between radicals. As long as polymerisation conditions are carefully selected and optimised, high conversions and low dispersities can be achieved.

1.4.1. Reversible Addition Fragmentation Chain Transfer Polymerisation (RAFT)

The key step of RAFT is the utility of a chain transfer agent to create a dynamic equilibrium (degenerative transfer) between active propagating radicals and dormant capped polymeric chains (Scheme 1.5).[37, 38]

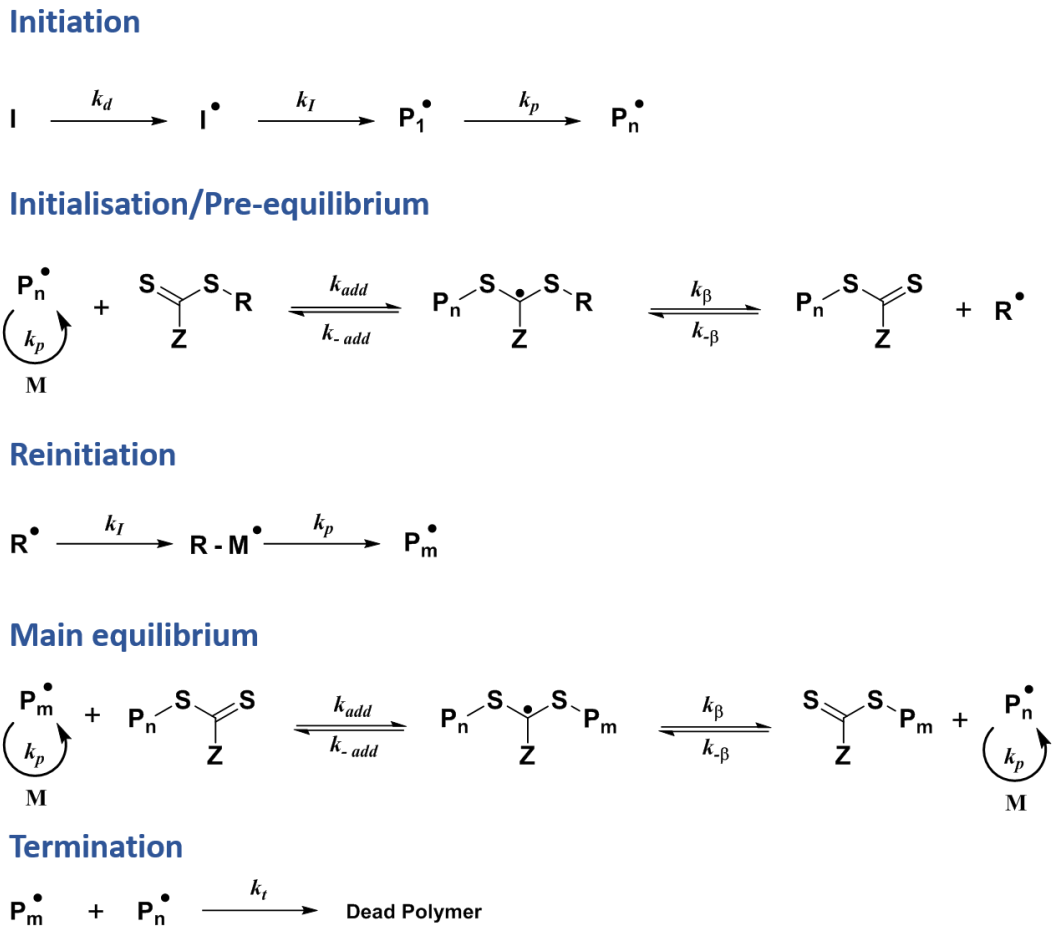


Scheme 1.5: The key step of RAFT polymerisation, the degenerate chain transfer mechanism.

This results in polymer chains all growing at comparable rates, hence yielding narrow molecular weight distributions. The history of radical addition fragmentation processes began in the 1970s, with a number of synthetic organic chemistry publications illustrating the S_H2 mechanism.[39] The use of addition fragmentation transfer agents was developed to control polymer molecular weight in the 1980s by Solomon *et al.*, who illustrated that the addition of a cyanoisopropyl radical to a poly(methyl methacrylate) macromonomer, resulted in a substantial reduction in the molecular weight of the polymers produced.[40-42]

Prior to 1995, all transfer events utilised were irreversible, such that the chain transfer event could occur only once per chain. This was overcome however by the development of a degenerate reversible chain transfer, whereby the product of the chain transfer is also capable of acting as a chain transfer agent and importantly it has similar activity.[38] This led directly to the discovery of RAFT polymerisation in 1998 by Graeme

Moad, Ezio Rizzardo and San Thang who utilised thiocarbonylthio compounds as CTAs, yielding narrow molecular weight distributions polymers with molecular weights close to theoretical (Scheme 1.6).[33, 43]



Scheme 1.6: The 5-step mechanism of RAFT polymerisation.

Initiation of a typical RAFT polymerisation utilises the thermal degradation of a conventional free radical initiator, for example azobisisobutyronitrile (AIBN), to generate primary radicals which then have the ability to propagate. In the pre-equilibrium step the propagating radical adds on to the chain transfer agent, which then fragments generating another primary radical (k_{add}) is the rate constant of addition and the k_β is the rate constant of fragmentation). This radical subsequently reacts with monomer forming another propagating chain.[44-46] This process then proceeds until either all monomer has been

consumed or until a termination event occurs. Termination is significantly suppressed, allowing for the synthesis of a range of complex macromolecules illustrated including stars, combs and multiblock copolymers.[43]

RAFT has been shown to be the most versatile RDRP system, with examples of both high activity (methacrylates, acrylates and acrylamides) and low activity monomers (vinyl acetate and *N*-vinyl pyrrolidone) polymerised, simply by matching the activity of the monomer to that of the RAFT agent (Figure 1.1).[43, 47] It is particularly challenging for other RDRP techniques to polymerise low activity monomers, so this is a major advantage of RAFT.

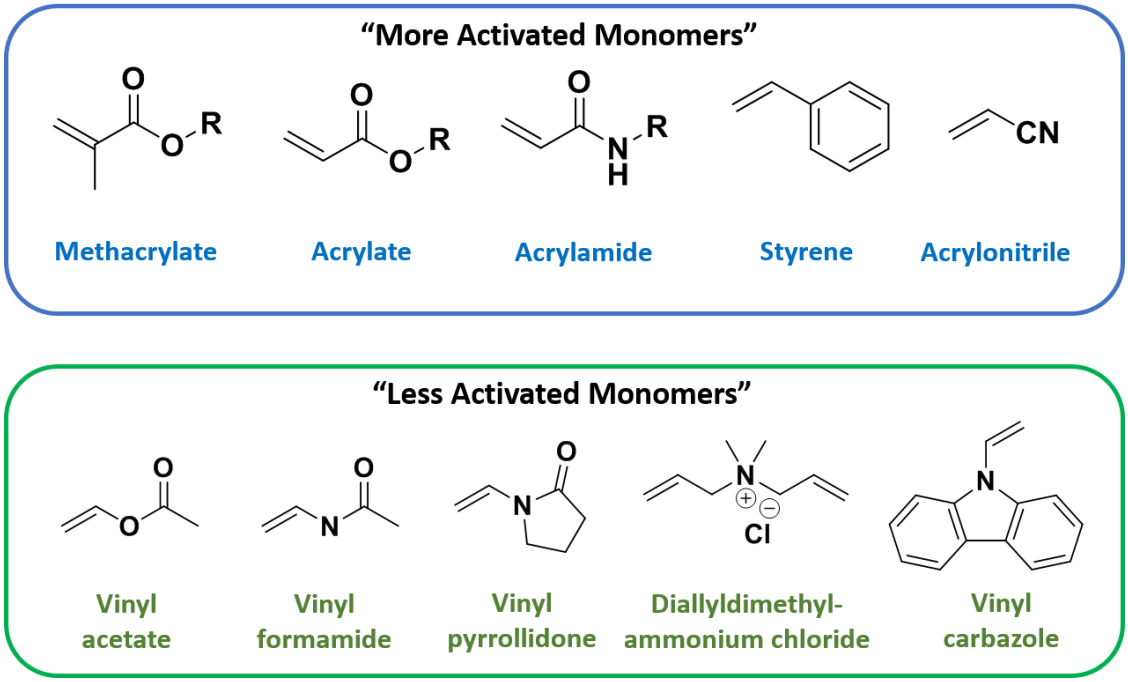


Figure 1.1: The categorisation of a diverse range of monomers in terms of their activity. More activated monomers have lower kp's and form more stable radicals in comparison to less activated monomers.

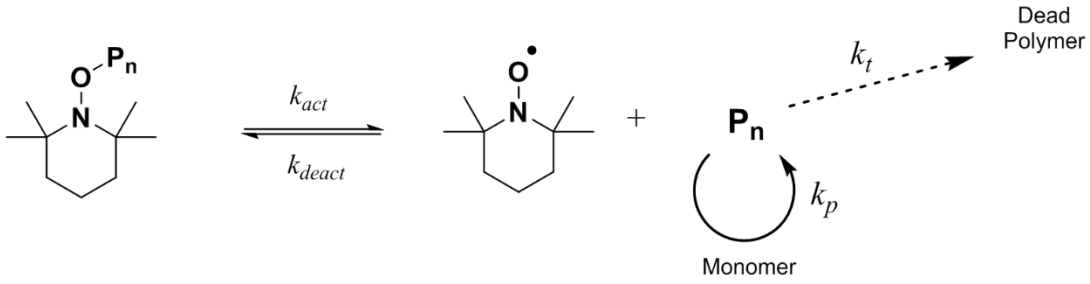
Other benefits of these polymerisation processes, are the simple reaction set ups, deoxygenation by inert gas bubbling and that metal catalysts can be avoided. However RAFT agents are typically brightly coloured and end cap the polymer chains. This means that the polymers produced can be discoloured and subsequent degradation of these thiol end groups can lead to undesirable odours.[48] Further end group modifications of the

polymers produced are often carried out, so to avoid this problem.[49] The synthesis of many RAFT agents also require multistep procedures, which can be time consuming and difficult to apply to industry.[50]

Alternatively sulfur-free RAFT emulsion polymerisation has been developed which utilises a macromonomer, macro chain transfer agent (synthesised by CCTP) as a chain transfer agent, to synthesise well defined multiblock copolymers.[51] This overcomes the issues associated with sulfur based chain transfer agents used in a typical RAFT polymerisation, but has much more limited monomer scope and efficiency.[52, 53]

1.4.2. Nitroxide-Mediated Polymerisation (NMP)

NMP utilises a stable free radical as a trapping agent to reversibly bond to either an initiating or propagating radical, generating an equilibrium between the active species that has the ability to propagate and a dormant alkyloxyamine.[54] This equilibrium is strongly pushed to the dormant state, so the concentration of radicals at any point is kept low, yielding a controlled polymerisation and well defined materials (Scheme 1.7).[55, 56]



Scheme 1.7: The mechanism of NMP, illustrating the equilibrium between dormant alkyloxyamine species and the active propagating radical.

NMP was first reported by David Solomon, Ezio Rizzardo and Paul Cacioli in 1985 and the patent is now one of the ten most cited in the history of chemistry.[34] The first report illustrated that by heating an alkyloxyamine with methyl acrylate in bulk at 80 °C, oligomers DP = 7 could be synthesised with monomer inserted into every alkyloxyamine. Due to the additional stability of the inserted products, no further reaction

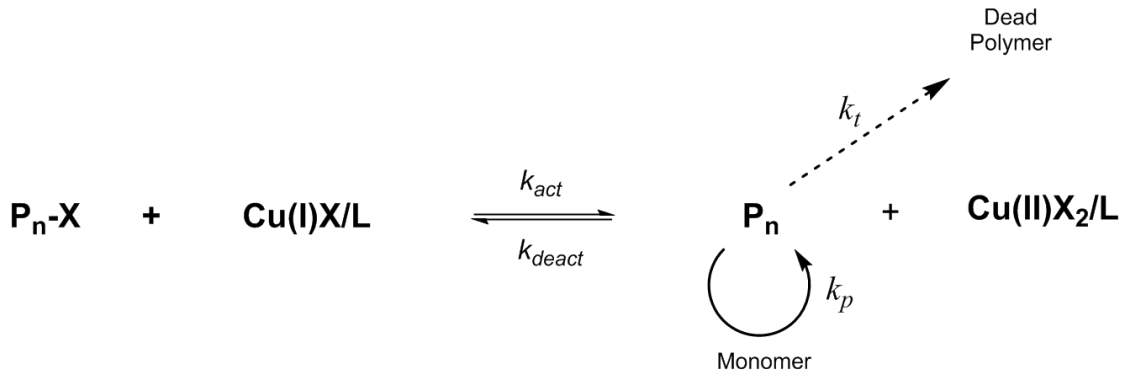
was illustrated even with longer reaction times. However, simply by increasing the temperature to 120 °C, reversible dissociation occurred, resulting in a successful polymerisation and a polymer of 70 units in length ($M_{n\,(SEC)}$ = 6700, $Đ$ = 1.82 *via* Size Exclusion Chromatography (SEC)) within 1.5 hours. Low molecular weight polystyrene (DP 12) was also successfully synthesised at 100 °C within 2 hours.[34] This technique was further been developed by Georges *et al.* who demonstrated the use of 2,2,6,6,-tetramethylpiperidinyl-1-oxy (TEMPO) as the nitroxide and benzoyl peroxide as the initiator, to synthesise well-defined poly(styrene-*co*-butadiene) with a low dispersity.[57, 58] This discovery brought NMP to the attention of the wider polymer community,[59] with reports by Hawker who illustrated significantly higher molecular weights and developed a number of new alkyloxyamines (including TIPNO and SG1),[60, 61] Fukuda who demonstrated enhanced rates by controlling the nitroxide concentration[62, 63] and Fischer who completed detailed kinetic studies.[64]

NMP has significant advantages in terms of the simplicity of the procedure and the high purity of the polymers produced (absence of both metals and thiols).[55, 56] There are however a number of challenges that remain, including a limited monomer compatibility. Reaction rates are generally slow, and not only require high temperatures (typically 120-145 °C) but also long reaction times (1-3 days) to achieve high conversions. Reactions are susceptible to side reactions, which can limit the achievable molecular weight and broaden the dispersity of the polymers produced.[65] In particular there are significant challenges in the polymerisation of methacrylate monomers, which has been attributed to the slow recombination of nitroxides with sterically hindered propagating polymethacrylate radicals, and also to the disproportionation side reactions between these radicals.[66-68] To date the best method to overcome these issues is to copolymerise methacrylates with a small amount of a more conventional NMP monomer

class, for example styrene or acrylonitrile.[69, 70] One other potential drawback of NMP is the added complexity of synthesising the nitroxide and alkyloxyamine species which may limit the applicability of these systems to industrial applications.[54]

1.4.3. Atom Transfer Radical Polymerisation (ATRP)

The key step of an ATRP reaction is the reversible abstraction of a halogen from a dormant initiator or polymer chain by a transition metal halide/ligand complex generating an active propagating radical. As in other RDRP processes, this equilibrium heavily favours the presence of the dormant species, maintaining a low radical concentration, resulting in polymer chains growing at an equivalent rate and termination minimised (Scheme 1.8).[36]



Scheme 1.8: The mechanism of ATRP utilising a copper catalysed system. X represents a halogen atom and L represents the ligand.

Transition metal mediated living radical polymerisation was independently discovered by Mitsuo Sawamoto and Krzysztof Matyjaszewski (who termed it ATRP) in 1995. Sawamoto utilised a ruthenium(II) catalyst to yield a controlled polymerisation of methyl methacrylate, whereas Matyjaszewski used a copper based system (a reversible redox reaction between Cu(I)Cl and Cu(II)Cl_2) to synthesise well-defined polystyrene.[35, 36] This technique has developed to encompass many other transition metals, (those with multiple oxidations states) including iron,[71] osmium,[72] nickel,[73] palladium,[74] silver,[75]

molybdenum[76] and zinc.[77] No other metal however has achieved better results than copper, which also has the advantages of being cheap and easy to handle.[78]

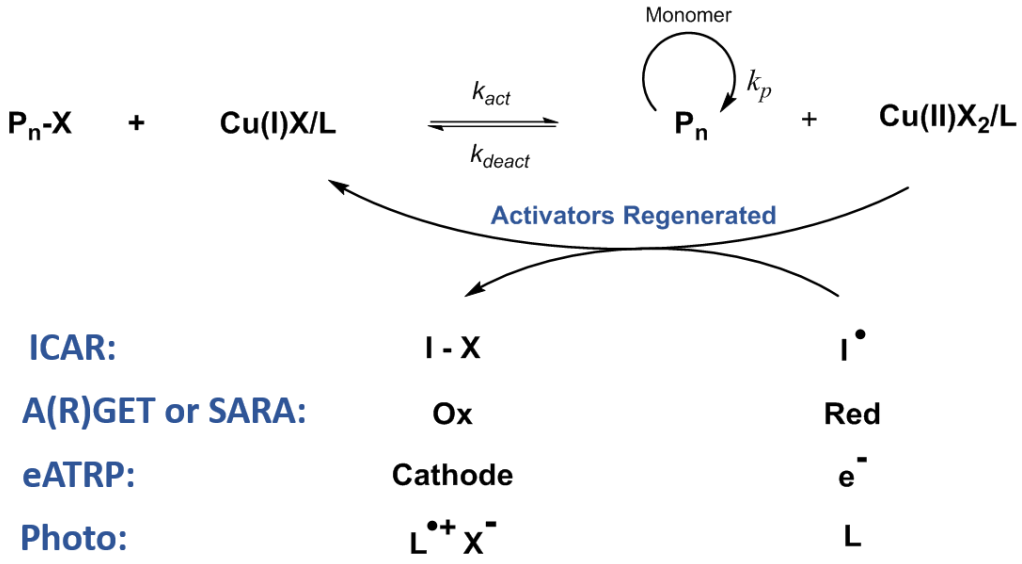
For a successful copper mediated ATRP to be achieved, an alkyl halide initiator, a nitrogen containing ligand (typically a bidentate or multidentate tertiary amine) and a copper(I) halide are required.[79] With the transition metal in its lowest oxidation state, the complex acts as an activating species, generating a radical which can subsequently propagate, and in its highest oxidation state the complex acts as a deactivating species, with the polymer chain capped by a halide. The selection of the appropriate combination of initiator and ligand for each polymerisation is of significant importance so to maintain the low concentration of radicals and to ensure initiation is much faster than propagation and control is therefore achieved.[80-83] As in all RDRP reactions termination is minimised but not eliminated. One advantage of ATRP is that the persistent radical effect (PRE) occurs during the early stages of polymerisation.[64] Small amounts of bimolecular termination occur, which generates the high oxidation state complex. This slight excess in deactivating species, pushes the equilibrium further towards dormant yielding extra control over the polymerisation and improved dispersities.[84, 85]

ATRP has been developed to encompass a broad range of chemical functionalities and architectures, with the generation of star polymers from multifunctional initiators being a notable achievement.[86-89] There is no doubt the main challenge associated with conventional ATRP is the presence of high concentrations of transition metal complexes in the polymers produced, with one or more equivalent of the Cu(I) salt relative to the initiator commonly required to maintain a satisfactory rate of polymerisation.[90, 91]The polymers typically have a dark brown colour prior to purification and metal residues could limit the applicability of these polymers in certain applications.[92, 93] The successful monomer pool for ATRP is also much more limited in comparison to RAFT, high

temperatures are commonly utilised for polymerisation (80 °C to 110 °C) and reactions typically have to be stopped at moderate conversions (~40%) so to maintain control over the molecular weight distribution and to preserve high end group fidelity. Therefore in the synthesis of a block copolymer, the homo-polymer must be purified, and then a second polymerisation set up with this macroinitiator.[77] The limitations of conventional ATRP have resulted in the development of a number of new methods which utilise external additives or stimuli, which are explored in the subsequent section.[94-96]

1.4.3.1. Alternative Low Copper Concentration Approaches

Efforts to reduce catalyst loadings has led to the development of a number of different activator regeneration processes by Matyjaszewski and co-workers, with the use of reducing agents, the addition of a free radical initiator, or the use of external stimuli for example light or electrochemical potential illustrated (Scheme 1.9).[97] These methodologies have increased the scope of potential materials, with the *in situ* synthesis of multiblock copolymers a notable achievement.[98]



Scheme 1.9: Methods of activator regeneration via ATRP, illustrating ICAR, A(R)GET, SARA, photo and eATRP.

Initiators for continuous activator regeneration (ICAR) ATRP, was developed in 2006 and utilises an additional component: a conventional free radical initiator, which continuously regenerates the active species by abstracting a bromine from a Cu(II)Br_2 deactivating species generating Cu(I)Br species.[99] Compared to conventional ATRP significantly lower concentrations of catalyst can be used with ICAR ATRP, with quantities typically around 100 ppm. There are however challenges associated with the unwanted generation of radicals from the free radical initiator and subsequently their propagation which limits the scope of potential materials that can be prepared.[94]

The substitution of a free radical initiator for a reducing agent overcomes this problem. Activator generated by electron transfer (AGET) ATRP utilises a reducing agent,[100] commonly ascorbic acid,[101] tin(II)-2-ethylhexanoate,[102] glucose[103] or hydrazine[104] to react with Cu(II)X_2 complexes regenerating the active Cu(I)X species. This methodology was developed into activators regenerated by electron transfer (ARGET) ATRP,[96] which utilises the same reducing agents, but crucially they are slowly fed into the reaction during the polymerisation. This again allows for much lower copper concentrations to be successfully utilised without compromising control over the polymerisation.[105, 106]

External stimuli have been utilised as alternatives to the addition of extra components, with the development of electrochemical and photo-mediated ATRP processes.[107-109] These techniques have the additional advantage of providing spatiotemporal control, allowing the polymer chemist to switch "on" and "off" the reaction. Electrochemical ATRP (eATRP) was founded in 2011,[110] and utilises an applied potential (E_{app}) to gain significant control over the ratio of activated and deactivated species, and hence the polymerisation equilibrium between dormant species and propagating radicals.[111, 112] The rate of polymerisation can simply be controlled by

changing the potential of a working electrode. Temporal control can also be achieved by switching the potential "on" and "off" so the polymer can be modified or addition reagents or monomers can be added to the reactions whilst in this dormant state, limiting termination events and preventing the loss of any active chains.[113] Thus eATRP has proven to be a very desirable system, for the synthesis of a broad range of well-defined macromolecules.[108, 114]

Photochemical mediation has also attracted considerable interest, with Yusuf Yagci developing the first copper mediated photosystem in 2011.[115] Free ligand, in this case PMDETA in solution reduces $Cu(II)X_2$ to Cu(I)X when in a photo-excited state. Polymerisation control and a chain extension were illustrated but issues with the insolubility of $Cu(II)Br_2$ in bulk was observed and it was only possible to achieve moderate conversions.[115] Significant advances in this chemistry have been achieved with recent reports by Matyjaszewski, Haddleton and Junkers in particular, illustrating a diverse range of polymers with high end group fidelity even at near quantitative conversions, allowing for the synthesis of multiblock copolymers.[116-120] Similarly to eATRP, temporal control can be achieved by controlling light intensity and wavelength, which is another attractive feature for building a wider scope of polymeric materials.[121, 122]

Further developments to completely avoid the use of copper have recently been developed, with a "metal free" ATRP methodology first reported in 2014.[123] An organic photocatalyst, (rather than a metal complex) was utilised to yield a controlled polymerisation. It is worthy of note, however, that the successfulness of these systems has been limited, generally yielding lower conversions, broader molecular weight distributions and lower end group fidelity than analogous metal catalysed strategies.[124, 125]

1.4.4. Cu(0)-Reversible Deactivation Radical Polymerisation

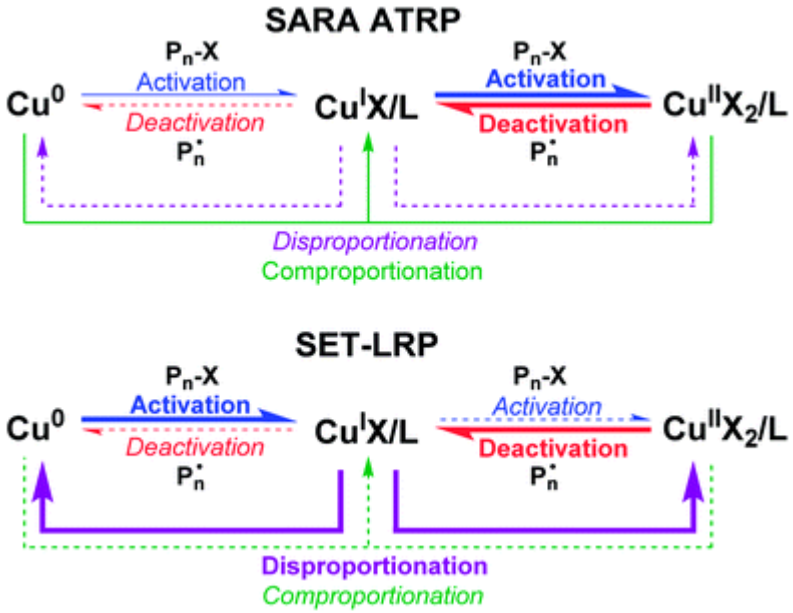
An individual section has been designated to Cu(0)-RDRP as this is the technique utilised for the synthesis of polymers throughout this thesis. The history of utilising zerovalent metals dates back to 1997, with Matyjaszewski illustrating that on the addition of Cu(0) or Fe(0) to a typical ATRP reaction, well defined polymers could be synthesised with a notably faster rate than when metal salts alone had been used. This was the first reported methodology of reducing catalyst loadings while maintaining narrow molecular weight distributions.[126] The synthesis of polyacrylates was notably particularly slow when only metal halide salts had been utilised, with the timescale of reactions in days. This was attributed to this polymerisation being less tolerant to the presence of Cu(II) species, in comparison to methacrylates or styrene, and in combination with a high activity polychloroalkane initiator significant deactivator was generated. On addition of Cu(0), there was a rapid enhancement of polymerisation rate (three times) without compromising control over molecular weight and dispersity.[127] This was attributed to the reduction of Cu(II) species back to Cu(I) thus reducing the excess of deactivator. Further reports by Percec illustrated the enhancement of rate on addition of Cu(0) metal,[128, 129] but all early reports utilised high temperatures, typically between 70 °C and 110 °C.[74, 130, 131]

The concept of Cu(0) mediating the polymerisation process, rather than supplementing the presence of Cu(I) salts, was first introduced by Percec and co-workers in 2002 utilising the disproportionation of Cu(I) salt in the presence of Tren ligand, to polymerise vinyl chloride in a two-phase system of water and tetrahydrofuran (THF). Low molecular weight polyvinyl chloride was synthesised and significantly this reaction could be performed at ambient temperature.[132] In 2006, Percec illustrated that Cu(0) powder (or wire) could be utilised as the catalyst for the polymerisation of acrylates,

methacrylates and vinyl chloride in the presence of a complex of Cu(II)Br_2 deactivator and tris[2-(dimethylamino)ethyl]amine (Me_6Tren) ligand.[133] This work was christened as single electron transfer living radical polymerisation (SET LRP) and expanded the scope of Cu(0) mediated polymerisation from water, to also encompass alcohols, dipolar aprotic solvents e.g. dimethyl sulfoxide (DMSO), ethylene and propylene carbonate and ionic liquids. Impressively, polymers could be synthesised with molecular weights in excess of one million molecular weight while maintaining a dispersity of less than 1.20. The reaction time was only 3 hours and again could be performed at ambient temperature or below.[133] This breakthrough has subsequently been the basis for many hundreds of publications,[134] illustrating a wide scope of well-defined functional materials and complex macromolecular architectures. Critical analysis of monomer scope and experimental components will be explored in sections 1.4.4.2-1.4.4.6.

1.4.4.1. Mechanistic Mention

The mechanism for Cu(0)-RDRP has been the result of rigorous debate since the SET LRP (single electron transfer living radical polymerisation) concept was proposed in 2006 with many publications examining this area.[135-137] Matyjaszewski and co-workers subsequently proposed the SARA (supplemental activator and reducing agent) ATRP model, suggesting that the polymerisation proceeds *via* the well reported ATRP mechanism.[138, 139] Even though both proposed models utilise the same components, there is significant differences in terms of the contribution of disproportionation versus comproportionation, and which copper species is the activator (Scheme 1.10). The SARA ATRP mechanism proposes that Cu(I) is the major activator of the alkyl halide initiator, with Cu(0) acting as a supplemental activator, that reduces the excess of Cu(II) species to Cu(I) species *via* comproportionation.[135]



Scheme 1.10: The mechanisms of SARA ATRP and SET-LRP, with the thickness of arrows indicating the contribution of a reaction to the mechanism. As shown in *Polym. Chem*., 2014, 5, 4396.

Conversely, SET LRP proposes that Cu(0) is the major activator and that Cu(I) species do not activate the alkyl halide initiators, but instead undergo instantaneous disproportionation.[140-142] The mechanism is a complex topic which is yet to be definitively resolved, but previous work by the Haddleton Group illustrates strong mechanistic differences (i.e. rate of disproportionation vs comproportionation) based on the nature of the monomer and solvent, and the concentration of ligand employed. For example in a DMSO:methyl acrylate mixture the extent of disproportionation of CuBr/Me_6Tren was suppressed to less than 10%, and the formation of Cu(0) particles did not result in a rapid increase in polymerisation rate.[136] These observations support the SARA mechanism over SET LRP, which has proposed instantaneous disproportionation and extremely reactive nascent Cu(0) particles. This is in contrast to reactions in pure water, where disproportionation of the same complex was shown to be near quantitative (~99%) and no comproportionation was observed, favouring the SET LRP mechanism.[137] Due to the complexity of this topic and that this thesis primarily employs this chemistry

to make novel materials (rather than offering mechanistic insight), the term Cu(0)-RDRP will be utilised.

1.4.4.2. Reaction Components: Monomer Classes

1.4.4.2.1. Acrylates

By far the most utilised monomer class in Cu(0)-RDRP is acrylates, with quantitative conversions, narrow molecular weight distributions (typical $Đ \sim 1.10$) and high end group fidelity illustrated.[143-146] Commonly, methyl acrylate is used as the basis of optimisation, but there are many other examples of successful syntheses, typically utilising EBiB as the initiator, Me_6Tren as the ligand and DMSO as the solvent.[147-149] Further developments have encompassed the synthesis of long chain alkyl monomers in a self-generating biphasic system,[150] semifluorinated monomers,[151, 152] functional monomers, for example glycidyl acrylate[153] and sugar monomers.[154]

1.4.4.2.2. Methacrylates

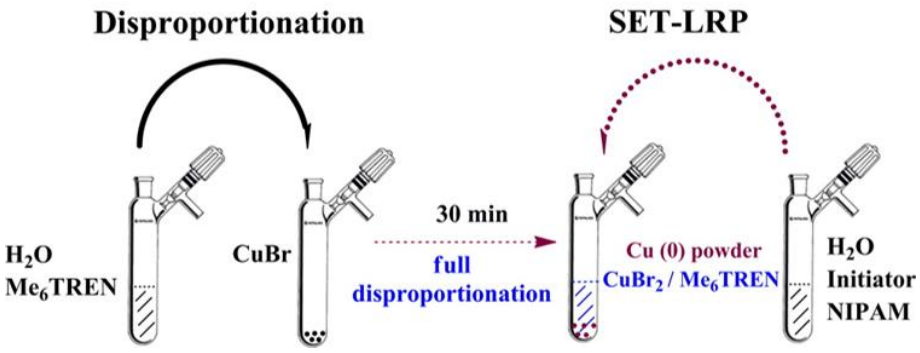
The application of Cu(0)-RDRP for the polymerisation of methacrylate monomers is more challenging than analogous acrylates, as the k_p of this monomer class is two orders of magnitude lower. There are still many reports which illustrate good levels of control but conversions are generally more limited and dispersities slightly broader ($Đ \sim 1.20$-1.30), limiting this technique from producing well-defined diblock copolymers. This is in contrast to the polymerisation of acrylates, where the synthesis of a range of multiblocks have been illustrated (please see section 1.4.4.7).

The synthesis of polymethacrylate homopolymers however has been well-illustrated, with Percec exploring the synthesis of poly(methyl methacrylate) (PMMA) with a range of initiators and solvent systems.[155-158] This work was extended to successfully encompass the synthesis of poly(ethyl methacrylate) (PEMA) and poly(butyl

methacrylate) (PBMA), as well as a range of fluorinated methacrylates.[150. 151. 159] There are challenges associated with polymerising methacrylate monomers in aqueous solution, with examples typically yielding controlled polymerisations but limited conversions and dispersities greater than 1.30,[160, 161] and also even though the chemistry has proven successful in polymerising semi-fluorinated monomers, only significantly broader dispersities (*Đ* ~ 2) have been achieved for highly hydrophobic methacrylate polymers, for example isobornyl methacrylate.[162, 163]

1.4.4.2.3. Acrylamides

The polymerisation of acrylamides *via* any copper mediated process has traditionally been particularly challenging with limited examples illustrating low conversions and broad dispersities.[164] In 2013, there was a significant development with the advent of aqueous Cu(0)-RDRP, a process by which Cu(I) in the presence of the ligand is disproportionated in aqueous solution prior to the addition of monomer and initiator, yielded well-defined poly(*N*-isopropyl acrylamide) (PNIPAm) in full conversion in less than 15 minutes (Đ ~ 1.10, ambient temperature, Scheme 1.11).[165]



Scheme 1.11: The procedure for SET-LRP via predisproportionation of CuBr/Me_6Tren in water adapted from *J. Am. Chem. Soc*., 135, 19, 7355.

The scope of this system has been expanded to the synthesis of many polyacrylamides with many protocols successful in yielding controlled polymerisations.[166-168] Pure water as a medium for ATRP has traditionally been

challenging, so this chemistry vastly increases the polymer chemists toolbox achieving accessibility to water soluble polymers including those that are charged, zwitterionic and acidic.[169-171]

1.4.4.2.4. Other monomer classes

There are a number of other monomer classes that have been successfully polymerised but further optimisation is required in all cases. There are limited reports of the synthesis of polystyrene, with Perrier and co-workers illustrating the best example with low dispersity (Đ ~1.20). However reactions were performed in toluene, (a solvent which typically stabilises Cu(I) species) at 90 °C.[172] The synthesis of poly(vinyl chloride) has also been illustrated, by Percec and co-workers, but the additional challenges of working with a gaseous monomer resulted in dispersities greater than 1.30.[173] Other monomer classes are particularly challenging, with control only achieved for polyacrylonitrile synthesis at limited conversions (~50%)[174] and the optimal dispersity achieved for poly(vinyl pyridine) greater than 1.50.[175]

1.4.4.3. Reaction Components: Organic and Aqueous Systems

There is a wide scope of solvents utilised in Cu(0)-RDRP, with solvent choice having a significant effect on whether Cu(I)Br (in the presence of a nitrogen containing ligand) is stabilised or disproportionation to Cu(0) and Cu(II)Br_2 is promoted. Often, there is a great deal of complexity in assessing whether a Cu(I) species or Cu(II) species is more stable, so numerous factors have to be considered. Cu(I) has a full shell of d electrons (d_{10}) generally forms tetrahedral geometry, whereas Cu(II) is d_9 so forms distorted octahedral geometries (Jahn Teller Effect).[176-178] In terms of solvents toluene, acetonitrile and dioxane are described as non disproportionating solvents, as they strongly stabilise Cu(I)Br, whereas DMSO, H_2O and alcohol solvents favour disproportionation

(to varying amounts) and are termed disproportionating solvents. Primarily disproportionating solvents have been utilised in Cu(0) mediated polymerisations, but these solvents in general are polar. A number of further polymerisation systems have therefore been developed, so to achieve the effective polymerisation of more hydrophobic monomers (in particular those not soluble in DMSO).[144, 179-182] It is well-known that the monomer must be soluble in the reaction solvent for a controlled polymerisation to be achieved, but it has recently been illustrated that the polymer produced doesn't necessarily have to be, with polymerisations able to proceed in biphasic systems, for example the polymerisation of butyl acrylate in DMSO or lauryl acrylate in isopropanol.[150, 183, 184] At a threshold degree of polymerisation the polymer is no longer soluble in the reaction solvent, and phase separation occurs, yielding this two layer system. Significantly the reaction can proceed while still maintaining control. Interestingly after the reaction is complete, one layer predominantly contains polymer, and the other contains catalyst, monomer and ligand, so purification of polymer from the catalyst can be achieved simply occur *via* decanting. Biphasic systems have been shown to maintain high end group fidelity and low dispersity, but there are limits observed in terms of attainable molecular weight.[183]

In non-disproportionating solvents, for example acetonitrile or toluene, successful homopolymerisations have been observed with linear kinetics and narrow dispersities, but end group fidelity is limited.[158, 185] A number of solvent mixtures have been developed to increase the scope of accessible materials, with the addition of a non disproportionating solvent to disproportionating solvents, for example toluene to methanol or acetonitrile to DMSO.[186, 187] Also the development of blood serum[188] and phosphate buffer solutions (PBS)[165] as potential media for biological applications have been successfully explored.

1.4.4.4. Reaction Components: Initiator Selection

The principles of initiation of Cu(0)-RDRP are the same as those of conventional ATRP (Figure 1.2).[189] To yield a controlled radical polymerisation, selection of the appropriate alkyl halide initiator is of upmost importance, so initiation is completed prior to propagation. This ensures that all polymer chains grow at the same rate so there is a smaller range of chain lengths thus a low dispersity. The activity of the initiator must be matched to that of the monomer, therefore high activity initiators which generate more stable radicals are typically utilised in the polymerisation of high activity monomers.[83] Ideally each initiator molecule should yield a polymer chain, thus initiator efficiency is full and the actual molecular weight achieved matches that which was targeted.

Many initiators can be utilised in the synthesis of well-defined polyacrylates, but most commonly ethyl-α-bromoisobutyrate (EBiB) and methyl-2-bromopropionate (MBP) have illustrated control polymerisations and dispersities around 1.10.[134, 142, 190, 191] In the synthesis of acrylamides typically water soluble tertiary radical forming initiators have been utilised, for example hydroxyethyl-α-bromoisobutyrate (HEBiB) and 3-dihydroxypropyl 2-bromo-methylpropanoate.[165, 166] Again many initiators have been explored in the synthesis of polymethacrylates but varying levels of success have been illustrated showing the importance of selection for this monomer class. Arguably tosyl chloride has yielded the best results to date, with linear evolution of molecular weight and narrow dispersity even at complete monomer conversion, but block copolymer reports are extremely limited.[152, 159] There are many further studies which explore the activities of different initiators and the effect on polymerisation.[192, 193]

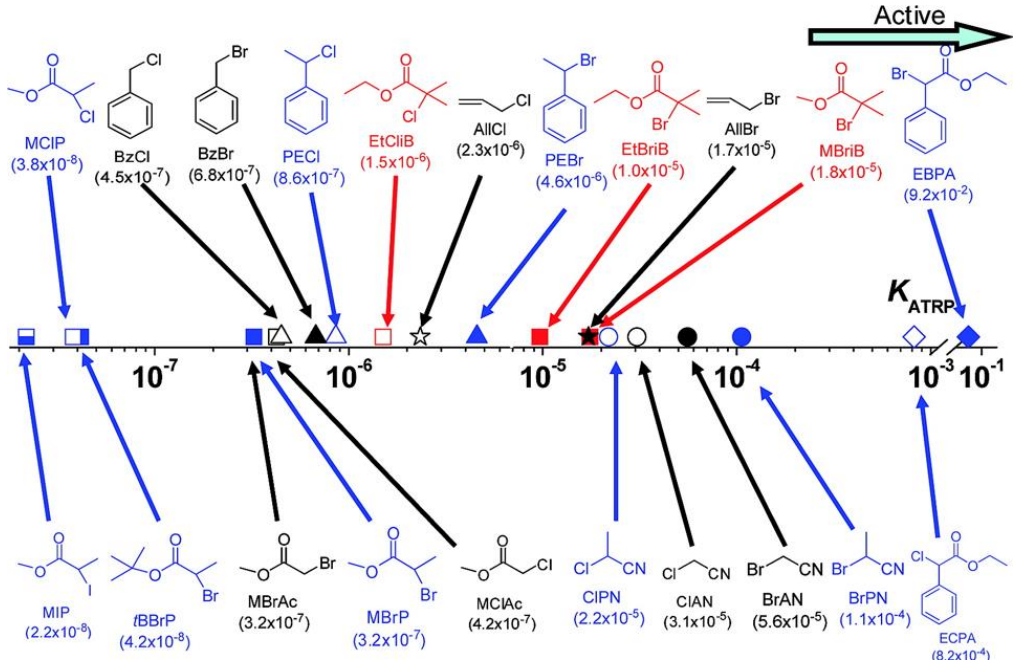


Figure 1.2: ATRP equilibrium constants for various initiators with Cu(I)X/TPMA (X = Br, Cl) in MeCN at 22 °C. Color key: (red) 3°; (blue) 2°; (black) 1°. Symbol key: (solid) R−Br; (open) R−Cl; (bottom-half-solid) R−I; (△) phenyl; (□) ester; (○) nitrile; (◇) phenyl ester; (☆) allyl. Figure as shown in *J. Am. Chem. Soc.*, 2008, **130** (32), 10702–10713.

1.4.4.5. Reaction components: Ligand Scope

The role of the ligand in copper mediated polymerisation is to solubilise copper salts, to donate or accept electrons from the metal and to tune the activity and hence effectiveness of the catalyst (Figure 1.3).[194] Nitrogen based ligands are optimal for these syntheses, with sulfur, oxygen and phosphorus based ligands illustrating different electronic effects and unfavourable binding constants.[78] Bidentate and predominantly multidentate ligands commonly promote successful polymerisation, with monodentate ligands resulting in an absence of polymerisation. The ability of a ligand to stabilise Cu(I) or Cu(II) salts determines its overall activity with σ-donating ligands, for example cyclam and Me_6Tren, strongly stabilising Cu(II) so classified as high activity, whereas π acceptor ligands, for example pyridinimines and bypridine, stabilising Cu(I) salts so are termed low activity.[82] High activity ligands are typically utilised to polymerise high k_p monomers for example acrylates and acrylamides, whereas low activity ligands are used to polymerise lower k_p monomers, for example styrene and methacrylates.[189, 195]

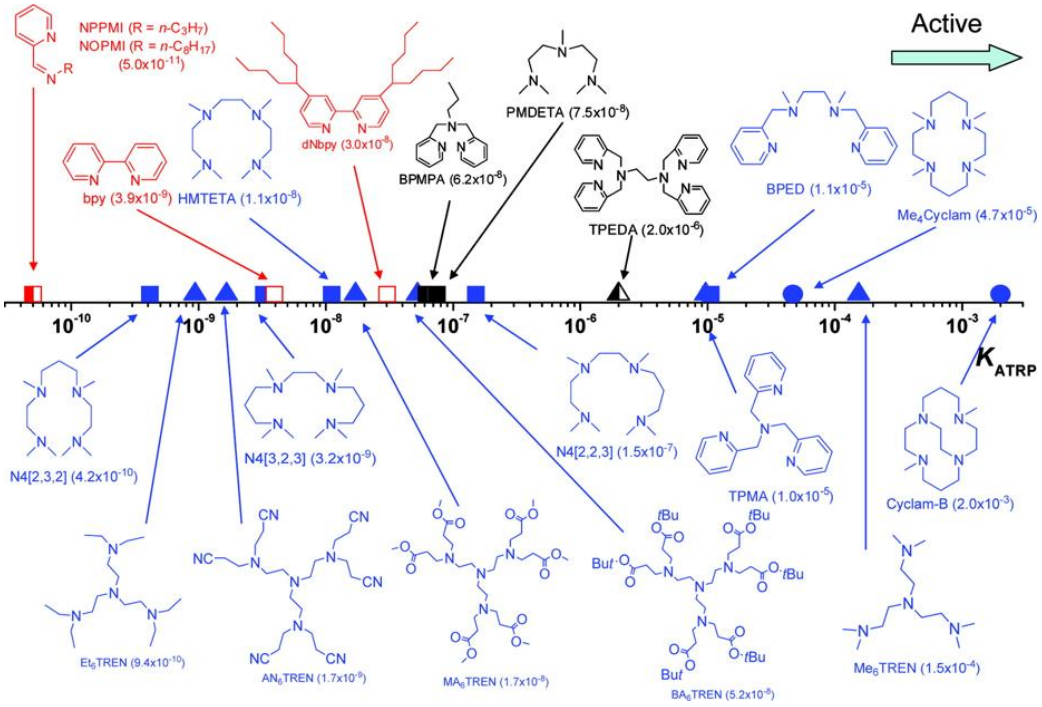


Figure 1.3: ATRP equilibrium constants KATRP for various N-based ligands with the initiator EBiB in the presence of Cu(I)Br in acetonitrile at 22 °C. Color key: (red) N2; (black) N3 and N6; (blue) N4. Symbol key: (solid) amine/imine; (open) pyridine; (left-half-solid) mixed; (□) linear; (Δ) branched; (○) cyclic. Figure as shown in *J. Am. Chem. Soc*., 2008, **130** (32), 10702–10713.

1.4.4.6. Reaction Components: Forms of Cu(0) and Activation Methods

Cu(0) powder was primarily utilised Cu(0)-RDRP and has been widely illustrated to facilitate controlled polymerisation maintaining end group fidelity and narrow molecular weight distributions (Figure 1.4b).[158, 181, 196] The effect of the Cu(0) particle size is important with smaller particles giving higher surface areas and hence greater rates of polymerisation.[197]

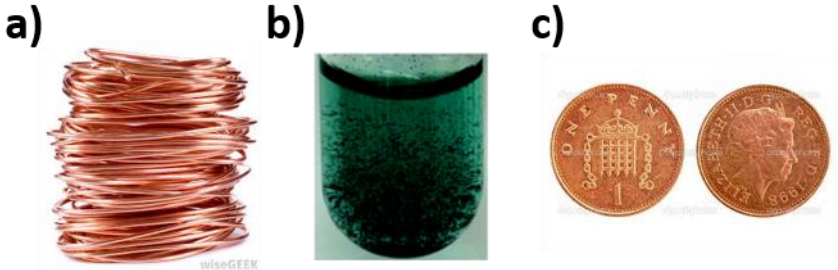
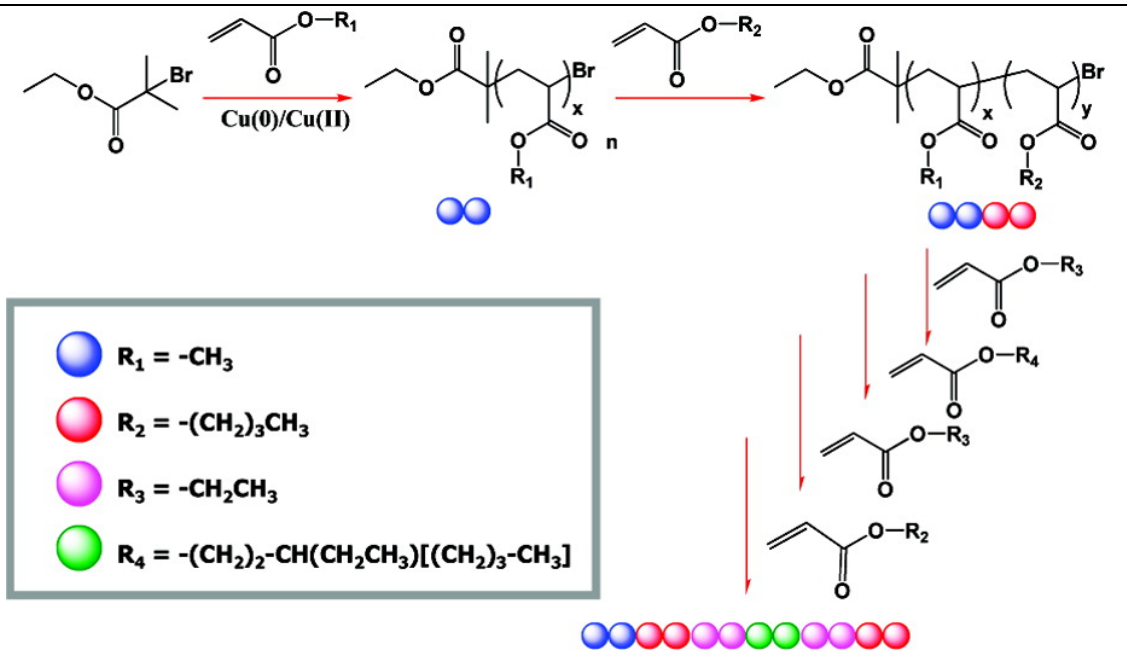


Figure 1.4: The different forms of Cu(0) utilised in Cu(0)-RDRP, with a) Cu(0) wire, b) Cu(0) particles and c) Cu(0) penny.

Cu(0) particles can also be produced from the disproportionation of Cu(I)Br in the presence of nitrogen containing ligand in DMSO and water.[165] These particles are much more active than commercially available particles yielding well-defined polymers in much shorter reaction times, typically less than 15 minutes. Cu(0) wire, (Figure 1.4a) however, has recently been further explored, as it provides easy preparation and purification from the subsequent polymer, as well as greater predictability in terms of reaction rate. Typically in comparison to particles, wire provides significantly greater control over the molecular weight distribution.[134] Activation of wire is required to remove the layer of Cu_2O from the surface or an induction period is observed.[129] Prior to polymerisation the wire can be activated using hydrazine under anaerobic conditions[134] or simply by dissolution in a concentrated acid (e.g. hydrochloric or glacial acetic acid).[198] Both methodologies result in the absence of an induction period and yield narrow molecular weight distribution polymers. Interestingly, it has been illustrated by Percec and co-workers that the fluorinated solvents trifluoroethanol (TFE) and tetrafluoropropanol (TFP) have the ability to self-activate the Cu(0)-wire, resulting in an absence of induction period and an enhancement in the rate of polymerisation in comparison to non-activated wire, while retaining high end group fidelity.[199] It has recently also been successfully reported that the copper wire can be substituted for a one penny copper coin (Figure 1.4c).[200]

1.4.4.7. Advanced Polymeric Materials

The accessibility of complex architectures is a major advantage of Cu(0)-RDRP with a wide range of polymeric materials synthesised. As previously discussed the synthesis of polyacrylates and polyacrylamides have both been successfully optimised with high end group fidelity maintained even at quantitative conversions allowing access to a range of well-defined multiblock copolymers (Scheme 1.12).[167, 201]



Scheme 1.12: The synthesis of multiblock copolymers by sequential addition of Monomers without intermediate purification, adapted from *J. Am. Chem. Soc.*, 2011, 133 (29), 11128–11131.

Further complex macromolecules have been explored with multifunctional initiators illustrated to make well-defined star polymers in both single phase and biphasic systems.[202, 203] Interestingly, star-star coupling is minimised in the biphasic system, allowing access to higher molecular weight polymers.[184] Dendrimers have been prepared by alternating Cu(0)-RDRP polymerisation steps and thio-bromo click reactions[204] and branched polymers have been achieved by copolymerising methyl acrylate with the initiator containing monomer 2-(2-bromoisobutyryloxy) ethyl acrylate.[205] The polymers synthesised utilising Cu(0)-RDRP have been employed in a range of biological and technological applications, with notable achievements in the synthesis of glycopolymers,[154, 206] polymer protein conjugates,[207] antibacterial agents[208] and surface modified polymers.[209, 210] There are numerous other functional materials that can be prepared with this polymerisation methodology and many other potential areas of developments within this field.

1.5. Cationic Polymers

Polyamines have attracted considerable interest due to the presence of cationic nitrogen atoms that allow for pH tuning and the formation of pH responsive nanoparticle structures that self-assemble in aqueous solution.[211-213] These properties render polyamines a good candidate for a wide range of applications such as gene delivery,[214] drug delivery,[215, 216] tissue engineering,[217] waste water treatment[218], paper making[219] and cosmetics[220]. Gene delivery, the process by which genetic material is externally introduced into a host cell, is an area of particular recent interest, as cationic moieties have the potential to form electrostatic complexes with anionic biomolecules, for example nucleic acids or proteins.[221, 222] These polymers must keep the genetic material in tact as the polyplex transfects into host cells, prior to release into the cytoplasm. This genetic material can then enter the nucleus, resulting in transcription and subsequent translation of a protein. This methodology has been developed to treat genetic and malignant disorders, but gene therapy trials (for example XSCID-XI) have thus far have resulted in mutations and poor gene expression profiles.[223, 224]

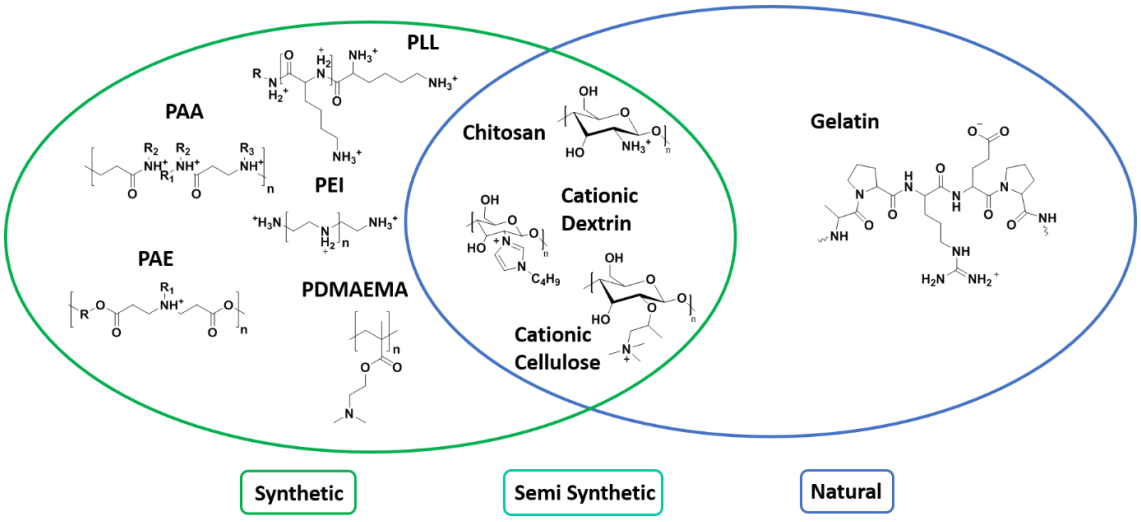


Figure 1.5: Common cationic polymers employed in gene delivery with synthetic, semi-synthetic and natural examples illustrated.

Cationic polymers have been extensively employed in gene delivery with numerous natural and synthetic examples[224-226] including amine functionalised polysaccharides,[227, 228] poly(L-lysine),[229] poly(amidoamines),[230] poly(amino-co-ester)s,[231, 232] poly(dimethylaminoethyl methacrylate) (PDMAEMA)[233] and most commonly poly(ethylene imines) (Figure 1.5).[234] Although these polymers can efficiently bind to RNA (ribonucleic acid) they are incapable of release due to the very high positive charge density and the lack of degradability of the polymer. Poly(dimethylaminoethyl acrylate) (PDMAEA) has recently attracted further interest due to its ability to provide a self-catalysed hydrolysis mechanism in water forming poly(acrylic acid) (PAA) and *N,N'*-dimethylaminoethanol.[235, 236] This process has been illustrated to allow genetic material to be released and is fundamental making the RNA available to trigger RNA interference (RNAi) processes.[237]

To exploit these desirable attributes of this polymer, many attempts have been made to synthesise well-defined PDMAEA, with several reversible-deactivation radical polymerisation methods employed, but in all cases polymerisation is problematic in comparison to other acrylate monomers, with significant side reactions and termination events commonly evident.[238] This is attributed to the nucleophilic nature of the tertiary amine functionality, and subsequent intramolecular and intermolecular reactions between propagating polymer chains. Current reports illustrate a maximum MWt of around 10000 g mol^{-1}, dispersities typically around 1.3 and 1.4 and a loss of end group fidelity, so bimodal distributions or significant tailing is observed when chain extension were attempted.[235, 237, 239, 240] Block copolymers in the literature therefore always incorporated PDMAEA as a low molecular weight final block. It is worthy of note that copper mediated RDRP methodologies have also had limited exploration in the synthesis of PDMAEA,

with the presence of secondary halides on the polymer chain end resulting in the potential for many further side reactions and termination events.[106]

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Chapter 2: Universal Conditions for the Controlled Polymerisation of Acrylates, Methacrylates and Styrene via Cu(0)-RDRP

Atom transfer radical polymerisation typically requires various parameters to be optimised in order to achieve a high degree of control over molecular weight and dispersity (such as the type of initiator, transition metal, ligand, solvent, temperature, deactivator, added salts and reducing agents). These components play a major role when switching monomers e.g. from acrylic to methacrylic and/or styrenic monomers during the synthesis of homo and block copolymers as the stability and reactivity of the carbon centred propagating radical dramatically changes. This is a challenge for both "experts" and non-experts as choosing the appropriate conditions for successful polymerisation can be time consuming and overall an arduous task. In this work we describe one set of universal conditions for the efficacious polymerisation of acrylates, methacrylates and styrene (using an identical initiator, ligand, copper salt and solvent) based on commercially available and inexpensive reagents (PMDETA, IPA, Cu(0) wire). The versatility of these conditions is demonstrated by the near quantitative polymerisation of these monomer families to yield well-defined materials over a range of molecular weights with low dispersities (~1.1-1.2). The control and high end group fidelity is further exemplified by in situ block copolymerisation upon sequential monomer addition for the case of methacrylates and styrene furnishing higher molecular weight copolymers with minimal termination. The facile nature of these conditions, combined with readily available reagents will greatly expand the access and availability of tailored polymeric materials to all researchers.

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2.1. Introduction

Both ATRP and Cu(0)-RDRP are considered as multicomponent systems typically composed of a metal source (Cu(I) or Cu(0)), a monomer (e.g. acrylates, methacrylates, styrene etc.), an initiator, a ligand, a solvent, a deactivator (e.g. $CuBr_2$, $CuCl_2$ etc.) as well as various other additives (e.g. salts, reducing agents etc.). To select the appropriate initiator, good knowledge of the reactivity of different alkyl halides towards initiation is important in order to maintain good control over the polymerisation process and the polymer end groups, the latter example being especially important for the efficient synthesis of block copolymers.[1-3] The selection of a suitable catalyst is also of importance as different reactivities can lead to vastly different rates of polymerisation (k_p), thus compromising overall control.[4] In addition the activity as well as the concentration of ligand plays an important role in the success of a polymerisation with ligands ranging from very high (e.g. tris(2-pyridylmethyl)amine (TPMA) and Me_6Tren) to very low activity (bipyridine (BPY), tetramethylethylenediamine (TMEDA)), where high activity corresponds to the ligands ability to stabilise Cu(II) relative to Cu(I).[3-5] Each class of ligand can facilitate the controlled polymerisation of different monomers, with typically highly active ligands providing good control in polymerising high k_p monomers (e.g. acrylates and acrylamides) and less active ligands achieving better control in the polymerisation of low k_p monomers (e.g. methacrylates), where ligands typically have low lying π^* orbitals capable of accepting electrons from the metal stabilising Cu(I).[1] However, it should be noted that active ligands have also been reported to mediate the polymerisation of methacrylates although no evidence of end group fidelity is provided.[6-7] Finally, although solvent choice certainly has a much lower impact on radical polymerisations (in terms of both rate and stereochemistry) as opposed to ionic polymerisations, the choice of the reaction medium can still significantly affect the ATRP

equilibrium and relevant rate constants.[1] Similar findings have also been observed in Cu(0)-mediated processes, where the results vary depending on the catalyst, ligand, solvent and monomer structure employed.[8] As such, it is necessary that all these components are judiciously matched (on top of adjusting other parameters such as temperature, dilution or reaction time) depending on the targeted monomer type (e.g. acrylates, methacrylate, styrene etc.) in order to yield controlled polymerisations with high end group fidelity (Figure 1). In contrast, research in the area of RAFT polymerisation has made more progress towards the development of universal chain transfer agents, potentially due to the simpler overall system.[9-11]

Even after careful optimisation of the reaction conditions of copper mediated ATRP, in order to maintain high end group fidelity one often has to stop the polymerisation at moderate/low conversions (e.g. 60%) and extensively purify the macroinitiator product prior to performing a chain extension experiment which is a waste of materials and time consuming, limiting commercial exploitation and attractiveness. In order to circumvent this, a number of different "variations" of ATRP have recently been developed, including use of free radical initiators[12], reducing agents[13, 14], electrochemical[15] and light stimuli[16-22] as well as Cu(0)-wire and Cu(0) particle mediated processes.[23, 24] The latter two approaches have demonstrated high end group fidelity even at near-quantitative conversions as exemplified by the *in situ* synthesis of multiblock copolymers.[25-31] Moreover, to the best of our knowledge, *in situ* chain extensions with copper mediated polymerisation approaches have only been reported for relatively high k_p monomers such as acrylates, as methacrylates exhibit much lower propagation rates. Importantly, all these techniques are capable of polymerising specific families of monomers, however choosing the appropriate method depending on the targeted polymer can also be challenging.[4]

Considering these issues it becomes evident that tuning reaction conditions for different monomer classes can be challenging and time consuming. As such, a universal system where identical components (e.g. same initiator/ligand/solvent/catalyst) could be used for the controlled polymerisation of a range of highly relevant monomers (e.g. acrylates, methacrylates and styrene) under environmentally friendly conditions would be highly desirable. More importantly, these polymers should exhibit not only narrow MWDs but also high end group fidelity, capable of facilitating the synthesis of block copolymers *in situ*. (Scheme 1) In addition, as many ligands used for classical ATRP or SET LRP such as Me_6Tren or TPMA can be either expensive or require step-wise syntheses, utilising commercially available and inexpensive ligands such as *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) would also be advantageous.

In order to address all of these features this chapter investigates the controlled polymerisation of acrylates, methacrylates and styrene utilising universal conditions (the same copper source, initiator, ligand and solvent). All the reagents are commercially available, inexpensive (e.g. PMDETA, copper source, solvent), "green" and easy to remove (isopropanol (IPA)) while the simple set up ensures accurate reproducibility. Under these carefully selected universal conditions acrylates, methacrylates and styrene can be successfully polymerised furnishing materials with high end group fidelity and narrow molecular weight distributions. Importantly, polymethacrylates and polystyrene can be successfully chain extended *in situ* upon sequential monomer addition forming diblock copolymers with low dispersities. This allows facile access to well-defined materials by both "experts" and non-experts for the first time.

2.2 Results and Discussion

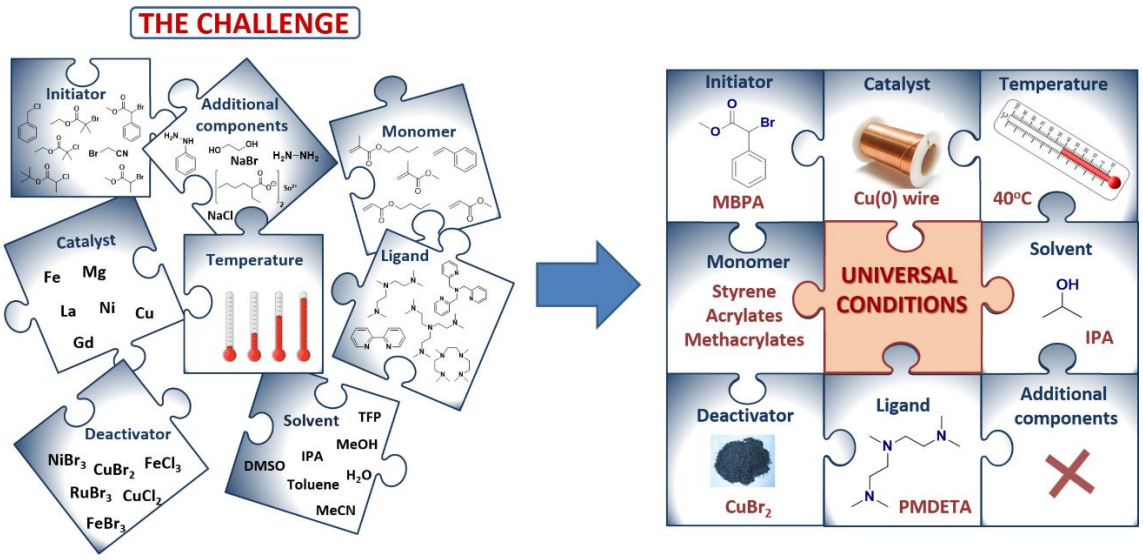


Figure 2.1: Schematic representation of the challenges typically encountered when conducting copper mediated polymerisations and our universal approach that can facilitate the polymerisation of styrene, acrylates and methacrylates.

2.2.1. Methyl Methacrylate, Evaluating Optimisation towards Universal Conditions

Cu(0)-wire mediated polymerisation is frequently employed for the controlled polymerisation of acrylates (e.g. methyl acrylate) at ambient temperature often utilising ethyl α-bromoisobutyrate as the initiator, Me_6Tren as the ligand and DMSO as the solvent yielding poly(acrylates) with narrow molecular weight distributions and near-quantitative conversions.[32] A small amount of $CuBr_2$ deactivator is also typically added in order to improve the control over MWDs.[33] However, under identical conditions the polymerisation of methyl methacrylate (MMA) resulted in a much slower polymerisation rate reaching 77% conversion (overnight) and the MWD was broad ($Đ \geq 1.5$) (Table 2.1, Entry 1 and Figure 2.10a). Increasing the temperature from 25 °C to 40 °C gave no improvement over the conversion or the control over the MWD ($Đ \geq 1.76$), which demonstrates that this combination of initiator, solvent, ligand cannot facilitate the controlled polymerisation of MMA (Table 2.1, Entry 2 and Figure 2.10b). This is because the initiating methacrylate radical (tertiary radical) has a similar stability to the

propagating radical (also a tertiary radical), whereas the acrylate radical is less stable (secondary radical). For control to be achieved initiation must be complete prior to propagation, therefore the acrylate polymerisation was controlled, yet the methacrylate polymerisation resulted in a broad dispersity. It should be noted however that EBiB has previously been reported to polymerise methacrylates via ATRP, but this can only be achieved when very low activity ligands are utilised. These pyridinimine ligands result in both initiation and propagation rates being significantly low enough so control can maintained.

Methyl-α-bromophenylacetate (MBPA) is a much less explored initiator,[34-36] which forms a more stable radical than EBiB due to resonance stabilisation of the phenyl ring. This initiator is considered highly active and is thus considered a suitable candidate for the polymerisation of methacrylates, given they are considered active monomers.[1] Significantly, MBPA gave rise to low dispersities ($Đ \sim 1.15$) although the conversion did not exceed 79% (overnight) even when the temperature was increased to 40 °C (Table 2.1, Entries 3-4 and Figure 2.10c-d). Regardless of the conversion, low dispersities clearly indicate that MBPA is an effective initiator for the controlled polymerisation of methacrylates under Cu(0)-mediated conditions resulting in fast initiation with respect to propagation. However, in all examples up to this point, DMSO is the solvent utilised and is a suitable solvent for the polymerisation of methyl methacrylate. However this solvent has previously been illustrated to result in uncontrolled reaction when the polymerisation of more hydrophobic monomers were attempted (i.e. any monomer more hydrophobic than butyl acrylate), so cannot act as a "universal" solvent.[32]

Table 2.1: ^{1}H NMR and SEC analysis of the polymerisation of MMA, with optimisation of solvent, ligand, temperature and ligand concentration shown.[a]

Entry	Initiator	Solvent	Ligand (% w.r.t [I])	Temp. (˚C)	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	Đ
1	EBiB	DMSO	Me_6Tren (18%)	RT	77	4100	7200	1.53
2	EBiB	DMSO	Me_6Tren (18%)	40	78	4200	6200	1.76
3	MBPA	DMSO	Me_6Tren (18%)	RT	79	4300	7800	1.15
4	MBPA	DMSO	Me_6Tren (18%)	40	62	3300	4600	1.26
5	MBPA	IPA	Me_6Tren (18%)	RT	<5	-	-	-
6	MBPA	IPA	Me_6Tren (18%)	40	25	1500	2500	1.68
7	MBPA	IPA	PMDETA (18%)	RT	57	3100	3800	1.16
8	MBPA	IPA	PMDETA (18%)	40	62	3300	4300	1.18
9	MBPA	IPA	PMDETA (36%)	40	98	5100	7000	1.18
10	MBPA	IPA	PMDETA (36%)	40	90	4700	6900	1.13
11	EBiB	IPA	Me_6Tren (36%)	40	79	4200	5700	1.76
12	EBiB	IPA	PMDETA (36%)	40	99	5200	6200	1.43

[a]In all polymerisations 5 cm of Cu(0) wire and 5% CuBr2 with respect to initiator were utilised and samples were taken after 18 hours. The volume ratio of monomer to solvent was maintained at 1:1 throughout. The target DP was 50 and conversion was calculated via ^{1}H NMR.

At that point, we envisaged isopropanol (IPA) as a potential alternative candidate for two main reasons. Firstly, IPA has already been shown to facilitate the controlled polymerisation of hydrophobic monomers (though only for acrylates) by forming a phase separation system (where monomer/catalyst are in a different layer to the polymer) with limited termination and side reactions.[37, 38] In addition, IPA is an

inexpensive "green" solvent (rated as class 3 by the international council for the harmonisation of pharmaceuticals for human health so has low toxicity and is generally accepted in pharmaceutical products),[39] which is easy to handle and can be removed by rotary evaporation (unlike DMSO). However, switching the solvent from DMSO to IPA (Me_6Tren, MBPA and temperature remaining the same) resulted in zero conversion being observed by either NMR (Nuclear Magnetic Resonance) or SEC, and increasing the temperature to 40 °C resulted in high dispersity polymer. ($Đ$ ~ 1.7) (Table 2.1, Entries 5-6 and Figure 2.10e-f). These results show that the combination of Me_6Tren with MBPA is unsuitable for the polymerisation of methacrylates under the selected reaction conditions.

Next we changed the ligand from the high activity tetradentate Me_6Tren to the lower activity tridentate PMDETA. Interestingly, there is significant differences in the geometry of the complexes formed between Cu(I) and Cu(II) salts and these ligands, with Cu(I) Me_6Tren complexes trigonal bipyramidal and Cu(II) Me_6Tren complexes trigonal pyramidal, whereas Cu(I) PMDETA complexes are tetrahedral and Cu(II) PMDETA complexes are square pyramidal. This can create significant differences in terms of whether Cu(I) or Cu(II) species are stabilised, creating significant changes in terms of control over the polymerisation. Interestingly, when this switch was made, narrow MWDs ($Đ$ ~ 1.16-1.18) could be obtained at either ambient or higher temperatures mirroring the results obtained from polymerisations in DMSO (where Me_6Tren was used instead of PMDETA, Table 2.1, Entries 7-8 and Figure 2.10g-h). Despite the success of these experiments, the final conversion was only 62% (after 18 h of reaction time) which precludes effective *in situ* chain extensions. In order to circumvent this, the concentration of the ligand was adjusted from 0.18 equiv. with respect to the initiator to 0.36 equiv. It has been previously reported by Percec, Matyjaszewski and Haddleton that relatively

small changes in ligand concentration can dramatically affect both the end group fidelity and the rate of the polymerisation.[32, 40-43] Indeed the aforementioned change of ligand concentration resulted in a remarkable acceleration on the rate of the polymerisation furnishing well-defined PMMA with a final dispersity of 1.18 at near quantitative conversion (98%) (Table 2.1, Entry 9, Figures 2.2 and 2.11). It should be noted that even lower dispersities can be achieved if the reaction is ceased at lower conversions (e.g. $Đ \sim$ 1.13 at 93% of conversion, Table 2.1, Entry 10). One important observation is that in all cases there is an observed discrepancy between theoretical and actual molecular weight by SEC, even though PMMA was being compared to PMMA standards. This is attributed to the loss of some initiator in the early stages of polymerisation either due to the high radical concentration associated with this high activity initiator or reactivity of isopropanol with the initiator. This therefore results in a higher molecular weight than targeted.

We were however, interested in the full capabilities of these universal conditions, including whether *in situ* chain extension could be achieved, so in all polymerisations conversions were pushed to as high a level as possible (near-quantitative conversions). The isolated materials were then initially analysed by MALDI-ToF-MS (matrix-assisted laser desorption/ionisation time of flight mass spectrometry) although no bromine could be detected attributed to MS fragmentation effects, in agreement with previous reports.[44-45] (Figure 2.12) However, when quantitative ^{13}C NMR was measured 94% of C-Br end groups could be observed, thus showing very high end group fidelity under these conditions (Figures 2.13 and 2.14). In order to further demonstrate the necessity to judiciously combine all the suggested components, MBPA was replaced by EBiB under our optimised conditions. However, broad MWDs were observed with either Me_6Tren or

PMDETA, thus highlighting the importance of our optimised conditions (Table 2.1, Entries 11-12 and Figure 2.10i-j).

2.2.2. Investigating the Scope of the Universal Conditions; Different DPs, Butyl and PEG Methacrylate and Block Copolymers

In order to probe the potential of this system in maintaining control over higher molecular weights we conducted a range of polymerisations targeting degrees of polymerisation from DP_n = 50-400. Under identical conditions four PMMA homopolymers were synthesised with molecular weight (MWt) varying from 7000 to 42000. In all cases ~90% conversion was reached with low dispersities ranging from 1.18 to 1.28 (Table 2.2 and Figure 2.2).

Table 2.2: ^{1}H NMR and SEC analysis of the polymerisation of methyl methacrylate at a range of DPs.[a]

Entry	DP_n	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	$Đ$
1[b]	50	98	5100	7000	1.18
2[c]	100	97	9900	14100	1.17
3[d]	200	95	19300	26100	1.28
4[d]	400	88	35500	42000	1.28

[a]In all polymerisations 5 cm of Cu(0) wire, 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised. Reactions were performed at 40 °C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated via ^{1}H NMR. [b]Reaction time 8 hours. [c]Reaction time 12 hours. [d]Reaction time 18 hours.

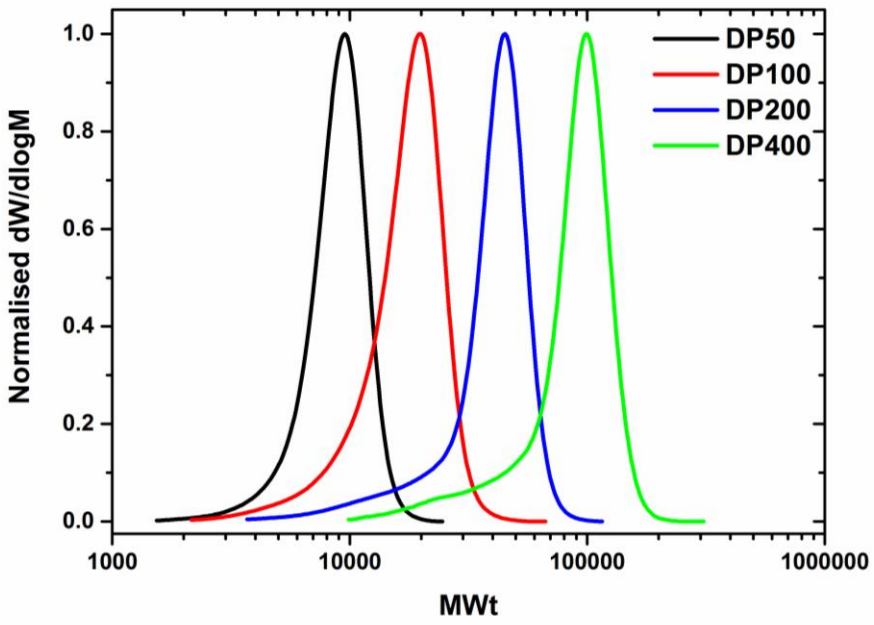


Figure 2.2: SEC analysis of PMMA synthesised via Cu(0)-RDRP showing DP_n = 50-400

In order to indirectly assess the end group fidelity of the system, *in situ* chain extensions of PMMA ($M_{n\,(sec)}$ = 7000, Đ = 1.18) with a second aliquot of MMA were also conducted furnishing higher MWt polymer ($M_{n\,(sec)}$ = 12800) without any increase in the initial dispersity of the macroinitiator. As the conversion of the second block was ~84% we managed to further increase this by the addition of another aliquot of ligand (together with the monomer addition) which yielded an increased conversion (92%) (Table 2.4, Entries 2-3 and Figures 2.4a and 2.15). Importantly, very little tailing in the low MWt region was observed by SEC suggesting an efficient re-initiation of PMMA and high end group fidelity under the selected conditions.

The scope of the system was subsequently extended to include a wide range of methacrylates, illustrating the ability of these conditions to facilitate the controlled polymerisation of both hydrophobic and hydrophilic monomers. Pleasingly, the polymerisation of the hydrophilic poly(ethylene glycol) methyl ether acrylate (PEGMA) led to narrow MWDs ($Đ$ ~ 1.11) at near quantitative conversion (~99%) with a final M_n of 27600 (Table 2.3, Entry 1 and Figures 2.3a and 2.16). It should be noted that in all

cases, methacrylate polymers synthesised were compared to PMMA standards, so there is a discrepancy in the molecular weights generated by SEC.

Table 2.3: ^{1}H NMR and SEC analysis of the polymerisation of a range of methacrylates (DP50) prepared via Cu(0)-RDRP.[a]

Entry	Polymer	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	$Đ$
1	Poly(ethylene glycol) methyl ether Methacrylate	>99.9	25200	27600	1.11
2	Butyl Methacrylate	97	5300	7200	1.22
3	Isobornyl Methacrylate	>99.9	11100	10200	1.10
4	Cyclohexyl Methacrylate	>99.9	8400	8300	1.10
5	Lauryl Methacrylate	99	12700	12300	1.13
6	Stearyl Methacrylate	>99.9	16900	17100	1.10

[a]In all homopolymerisations 5 cm of Cu(0) wire, 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 8 hours. Reactions were performed at 40 °C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated via ^{1}H NMR.

Butyl methacrylate was also successfully polymerised to afford a homopolymer with low dispersity ($Đ$ ~ 1.22) at ~ 97% of conversion (Table 2.3, Entry 2 and Figures 2.3b and 2.17). Interestingly, this system was further applicable to the polymerisation of very hydrophobic monomers, including isobornyl, cyclohexyl, lauryl and stearyl methacrylate. In all cases biphasic polymerisation systems were generated (please see section 1.4.4.3 for more detail), but with near quantitative conversions and narrow dispersities achieved. (Table 2.3, Entries 3-6, Figure 2.3c-f)

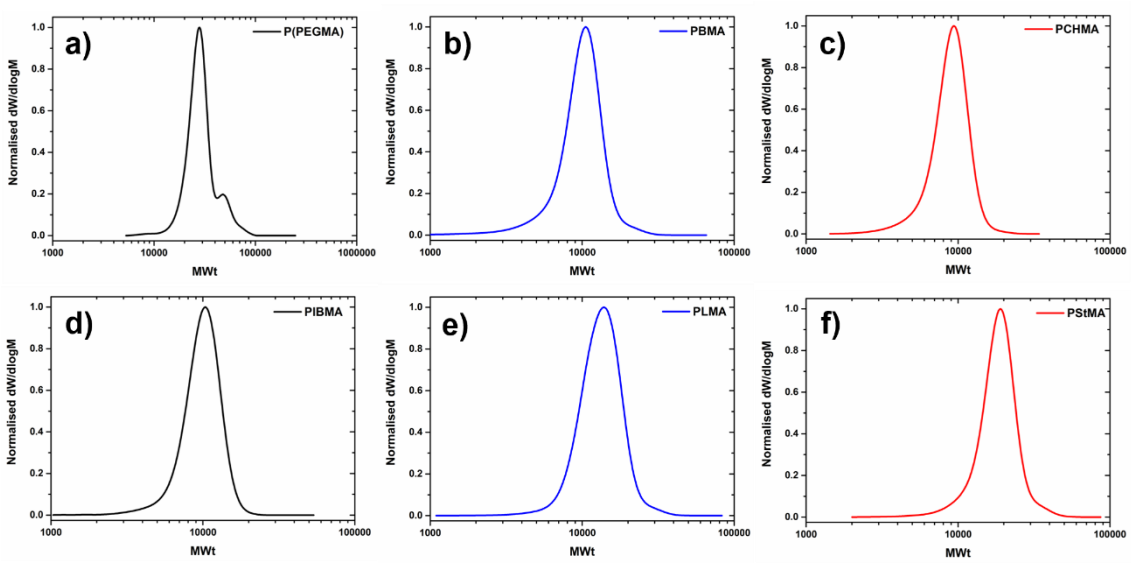


Figure 2.3: SEC analysis of polymethacrylates prepared via Cu(0)-RDRP in IPA at 40 ˚C under the following reaction conditions [MBPA]:[M]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.36].

Table 2.4: ^{1}H NMR and SEC analysis of the in situ chain extension of poly(methyl methacrylate) (DP50) with methyl and butyl methacrylate in IPA.[a]

Entry	Polymer	Target DP	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	$Đ$
1[a]	PMMA	50	97	5100	7000	1.18
2[b]	P(MMA-*b*-MMA)	50	84	9300	12800	1.18
3[c]	P(MMA-*b*-MMA)	50	92	9700	13000	1.19
4[c]	P(MMA-*b*-BMA)	50	99	12500	17200	1.20

[a]In homopolymerisations 5 cm of Cu(0) wire, 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 8 hours. Reactions were performed at 40 °C and the volume ratio of monomer to solvent was maintained at 1:1.The target DP was 50 and conversion was calculated via ^{1}H NMR. [b]Chain extension experiments utilised a 1:1 ratio of monomer to solvent [c]Chain extension experiments utilised a 1:1 ratio of monomer to solvent and 0.36 equivalents of PMDETA.

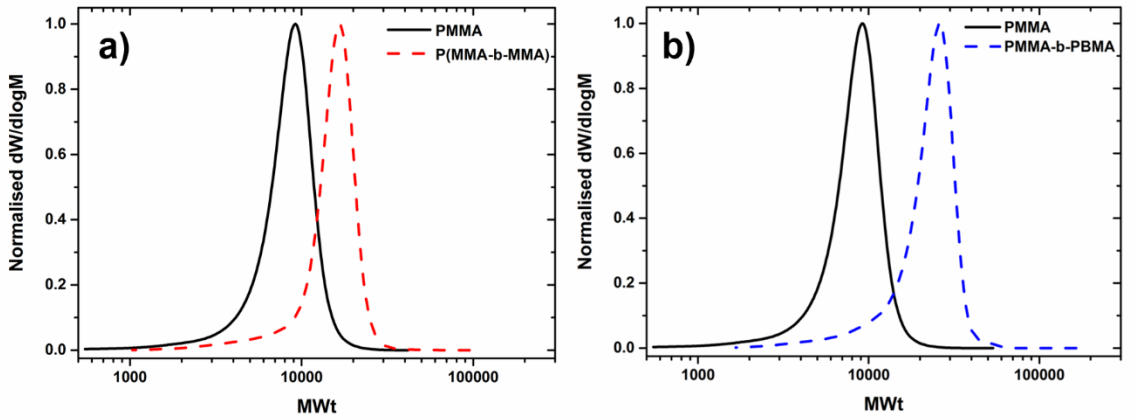


Figure 2.4: SEC analysis of the in situ chain extension of methyl methacrylate (DP50) with a) methyl methacrylate (DP50) and b) butyl methacrylate in IPA, with the addition of a 1:1 monomer to solvent ratio and also 1 equivalent of PMDETA.

The latter monomer (BMA) was also employed to *in situ* chain extend a PMMA macroinitiator yielding a well-defined p(MMA)-*b*-p(BMA) diblock copolymer with a final dispersity of 1.20 and a final M_n of 17200 (Table 2.4, Entry 4, Figures 2.4b and 2.18). Again, it should be noted that the conversion of the second block was also pushed to near-completion (~99%) with earlier samples yielding even lower dispersities. Overall, these results demonstrate that the combination of MBPA, IPA, PMDETA and Cu(0) wire can successfully mediate the controlled polymerisation of either hydrophobic or hydrophilic methacrylates yielding low dispersed polymers even at very high conversions leading to the *in situ* synthesis of well-defined diblock copolymers.

2.2.3. The Synthesis of Well Controlled Polystyrene under Universal Conditions

In the previous section the controlled polymerisation of methacrylates was demonstrated under the following conditions: [MMA]:[MBPA]:[PMDETA]:[$CuBr_2$] =[50]:[1]:[0.36]:[0.05] in 1:1 (v/v) monomer to solvent (IPA) ratio at 40 °C. However, when identical conditions were utilised to polymerise styrene, no conversion was detected by ^{1}H NMR spectroscopy or SEC (Table 2.5, Entry 1). It is interesting to note how one set of conditions provide quantitative conversions, high end group fidelity and low dispersities for one monomer family (methacrylates) but give rise to no conversion for

another family of monomer (styrene), further demonstrating the need for universal conditions. Significantly, by simply raising the temperature from 40 °C to 60 °C we obtained well-defined polystyrene exhibiting a narrow molecular weight distribution (*Đ* ~ 1.15) at 98% conversion (Figures 2.19c and 2.20). Similarly to the case of PMMA, the actual molecular weight was greater than that targeted which suggests this is inherently linked to this high activity initiator.

Table 2.5: ^{1}H NMR and SEC analysis of the polymerisation of polystyrene (DP50) via Cu(0)-RDRP, with optimisation of temperature and ligand concentration shown.[a]

Entry	Ligand (% w.r.t [I])	Temp. (˚C)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	*Đ*
1	PMDETA (18%)	40	0	-	-	-
2	PMDETA (18%)	60	58	3200	4100	1.16
3	PMDETA (36%)	60	98	5300	8100	1.15

[a]In all polymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ with respect to initiator were utilised and samples were taken after 36 hours. The volume ratio of monomer to solvent was maintained at 1:1 throughout. The target DP was 50 and conversion was calculated via ^{1}H NMR.

It is noted that with lower ligand concentration (0.18 equiv. with respect to the initiator) a slower polymerisation was detected reaching only ~ 58% of conversion under the same time scale of polymerisation (Table 2.5, Entry 2 and Figure 2.19b). Thus, for both methacrylates and styrene, increasing the ligand concentration (from 0.18 to 0.36 equiv.) results in a large increase in the conversion without compromising the MWDs (Table 2.5, entry 3). Although the polymerisation rate was low, requiring ~36 h to reach completion, high end group fidelity could be maintained throughout the reaction as evident by *in situ* chain extensions. Note however that similarly to previous reports, the MALDI-ToF mass spectrometry showed an absence of a bromine, but instead a double bond terminated polymer which is attributed to the loss of HBr during the ionisation of the silver salt[46-47] (Figure 2.21)

In order to demonstrate the presence of an active end group, a polystyrene homopolymer (98% conversion, $M_{n\ (SEC)}$ ~ 8100, $Đ$ ~ 1.15) was chain extended with another aliquot of styrene and an additional aliquot of PMDETA (consistent with the chain extension of MMA) resulting in a clear shift in the MWt by SEC and a final M_n of 17700 demonstrating high end group fidelity and low dispersity values (final $Đ$~ 1.24) (Table 2.6 and Figure 2.5).

Table 2.6: ^{1}H NMR and SEC analysis of the in situ chain extension of polystyrene (DP50) with styrene.[a]

Entry	Polymer	Target DP	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	$Đ$
1	PS	50	98	5300	8300	1.15
2[b]	PS-*b*-PS	100	47	10200	17700	1.24

[a]In homopolymerisations 5 cm of Cu(0) wire, 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. Reactions were performed at 60 °C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated via ^{1}H NMR. [b]Chain extension with a 1:1 ratio of monomer to solvent and 0.36 equivalents of PMDETA.

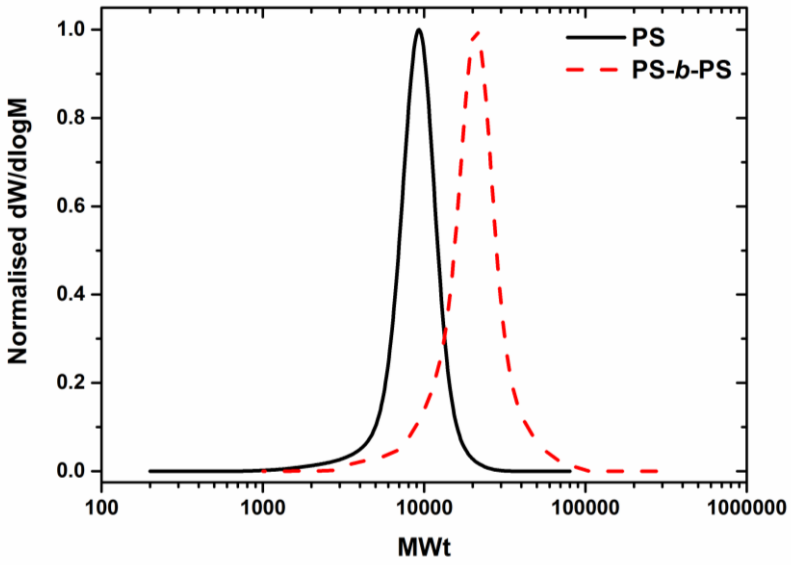


Figure 2.5: SEC analysis of the in situ chain extension of methyl methacrylate (DP50) with a) methyl methacrylate (DP50) and b) butyl methacrylate in IPA, with the addition of a 1:1 monomer to solvent ratio and also 1 equivalent of PMDETA.

Higher molecular weight polystyrene could also be targeted (DP_n = 100-400), with a final M_n of ~ 23900 and dispersity as low as 1.18 (Table 2.7 and Figure 2.6). These

results show that under the universal conditions both methacrylates and styrene can be successfully polymerised yielding low dispersity polymers. Near quantitative conversions and high end group fidelity could also be achieved when DP50 was targeted, capable of undergoing *in situ* chain extensions and block copolymerisations.

Table 2.7: ^{1}H NMR and SEC analysis of the polymerisation of styrene at a range of DPs.[a]

Entry	Target DP_n	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	$Đ$
1	50	98	5300	8100	1.15
2	100	80	8500	11700	1.17
3	200	55	11700	15800	1.15
4	400	36	15200	23900	1.18

[a]In all polymerisations 5 cm of Cu(0) wire, 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised. All reactions were performed at 60 °C with the volume ratio of monomer to solvent maintained at 1:1. The target DP was 50 and conversion was calculated via ^{1}H NMR. The reaction time was 36 hours.

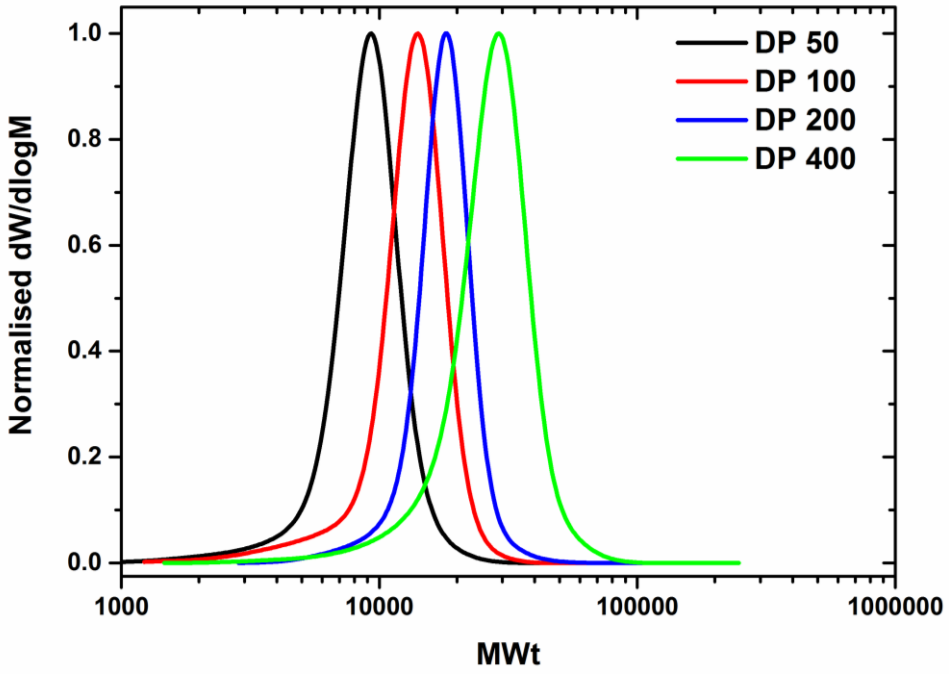


Figure 2.6: SEC analysis of PS synthesised via Cu(0)-RDRP showing target DP_n = 50-400.

2.2.4. The Synthesis of Well Controlled Polyacrylates under Universal Conditions

Our next target was to examine the polymerisation of acrylates. Arguably, the controlled polymerisation of acrylates is well documented in the literature with either Cu(0) or CuBr mediated systems presenting impressive end group fidelity as exemplified by the synthesis of multiblock copolymers.[48] EBiB or MBP, Me_6Tren and DMSO at ambient temperature are well-known as "ideal" conditions to polymerise MA. Under these conditions, and in agreement with the literature, > 99% conversion in a few hours can be achieved with dispersities as low as 1.06 (Table 2.8, Entry 1, Figure 2.23a).[27, 49, 50]

Table 2.8: ^{1}H NMR and SEC analysis for the polymerisation of methyl acrylate, with optimisation of solvent, ligand, temperature and ligand concentration shown.[a]

Entry	Initiator	Solvent	Ligand (% w.r.t [I])	Temp. (˚C)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	Đ
1	EBiB	DMSO	Me_6Tren (18%)	RT	>99.9	4500	5700	1.06
2	EBiB	IPA	Me_6Tren (18%)	RT	93	4200	5100	1.10
3	MBPA	IPA	Me_6Tren (18%)	RT	0	-	-	-
4	MBPA	IPA	PMDETA (36%)	RT	5	-	-	-
5	MBPA	IPA	PMDETA (36%)	40	10	-	-	-
6	MBPA	IPA	PMDETA (36%)	60	88	4000	5200	1.28
7	MBPA	IPA	PMDETA (18%)	60	90	4100	4600	1.15

[a]In all polymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ with respect to initiator were utilised and samples were taken after 18 hours. The volume ratio of monomer to solvent was maintained at 1:1 throughout. The target DP was 50 and conversion was calculated via ^{1}H NMR.

However, having a universal set of conditions and reagents that would allow for the controlled polymerisation of acrylates, methacrylates and styrene would be advantageous as it enables greater accessibility of polymeric materials by non-experts.

As such, we were initially interested to explore whether IPA could afford the controlled polymerisation of methyl acrylate (MA) (maintaining EBiB as the initiator and Me_6Tren as the ligand). As anticipated, the good control over the MWDs was maintained ($Đ$~ 1.10) with the reaction reaching > 90% conversion (Table 2.8, Entry 2 and Figure 2.23b). Nevertheless, EBiB was subsequently switched to MBPA (maintaining IPA, Me_6Tren and ambient temperature) but no conversion was observed under these conditions, which is attributed to the greater sensitivity of acrylate polymerisations to the presence of Cu(II)Br_2, which would be formed in combination with the high activity MBPA initiator (rather than the lower activity EBiB) as a result of the persistent radical effect. This could explain the absence of polymerisation of methyl acrylate in combination with MBPA. (Table 2.8, Entry 3).

Switching the ligand from Me_6Tren to PMDETA (0.36 equiv. with respect to the initiator) did not improve the outcome and no polymer was obtained (Table 2.8, Entry 4). However, when the temperature was raised from ambient temperature to 60 °C the polymerisation occurred yielding 88% of conversion and a dispersity of 1.28 (Table 2.8, Entries 5 and 6 and Figure 2.23c). Once more, it is quite remarkable how small changes in reaction conditions can result in a significant change in the results of the polymerisation. As it has already been reported that acrylates possess higher end group fidelity at lower ligand concentrations, the amount of PMDETA was subsequently decreased from 0.36 equiv. to 0.18 equiv. (with respect to the initiator) resulting in a decrease in the dispersity from 1.28 to 1.15, whilst also presenting a higher conversion (~ 90%) (Table 2.8, Entry 7, Figures 2.7 and 2.24). This result shows that methyl acrylate can also be successfully polymerised under the universal conditions utilising the inexpensive and commercially available ligand PMDETA, the more environmentally

friendly solvent IPA (in comparison to DMSO), MBPA as the initiator and ppm concentrations of copper.

Higher molecular weights of poly(methyl acrylate) (PMA) could also be obtained (DP = 100) although the dispersity value increased from 1.15 to 1.30 (Table 2.9, Figure 2.7). Nevertheless, butyl acrylate was also successfully polymerised with a dispersity of 1.28 at ~ 89% of conversion demonstrating the capability of the system to polymerise various acrylates (Figures 2.25-2.26).

Table 2.9: ^{1}H NMR and SEC analysis of the polymerisation of methyl acrylate at DP_n = 50-100.[a]

Entry	DP_n	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	$Đ$
1	50	90	4100	4600	1.15
2	100	81	7600	7500	1.30

[a]In all polymerisations 5 cm of Cu(0) wire, 5% $CuBr_2$ and 18% PMDETA with respect to initiator were utilised. Reactions were performed at 60 °C with the volume ratio of monomer to solvent maintained at 1:1. The target DP was 50 and conversion was calculated via ^{1}H NMR. The reaction time was 12 hours.

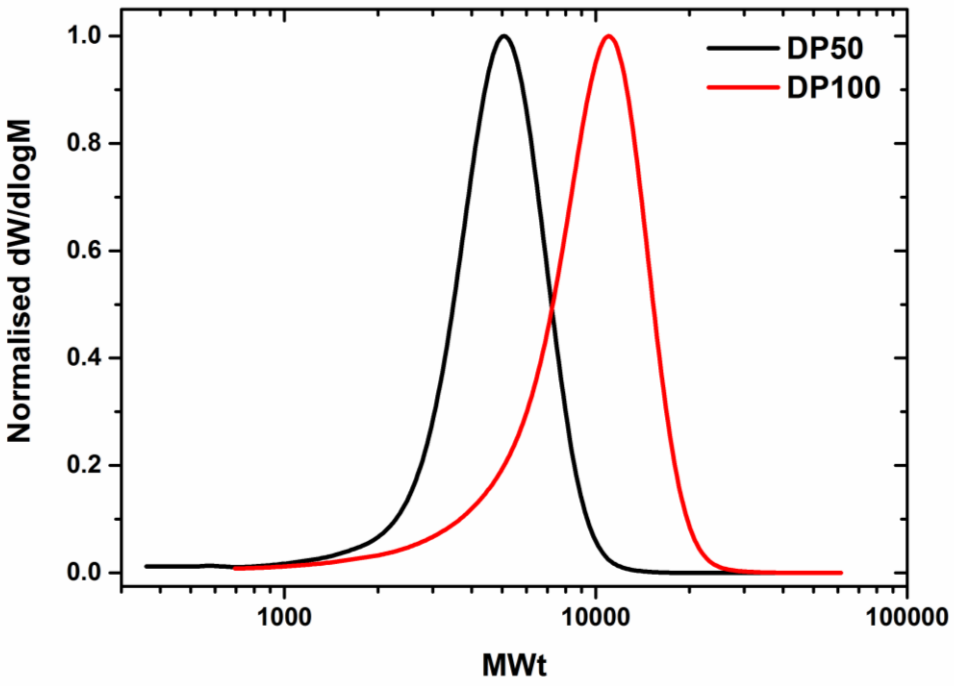


Figure 2.7: SEC analysis of PMA synthesised via Cu(0)-RDRP showing DPn = 50-100.

As conversions for the polyacrylates did not reach quantitative or near quantitative levels, *in situ* chain extensions were not attempted. However, MALDI-ToF-MS analysis revealed very high end group fidelity with the major polymer peak distribution corresponding to bromine terminated PMA (Figure 3).

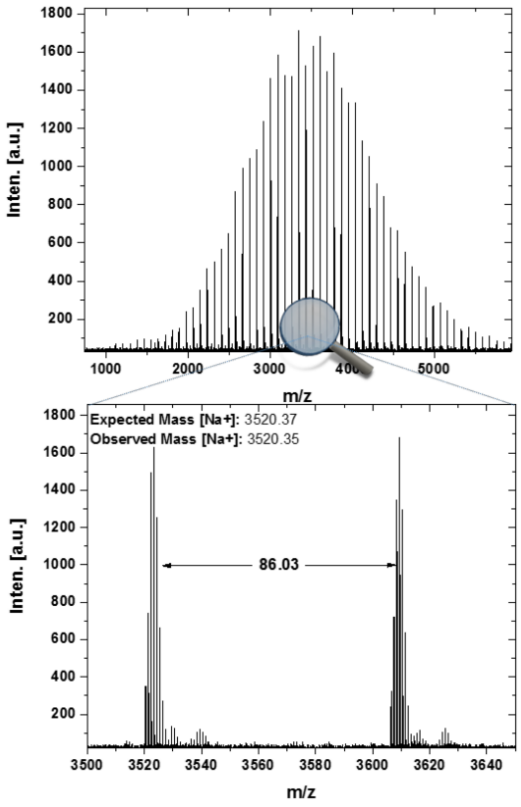


Figure 2.8: MALDI-ToF-MS spectra of PMA synthesised *via* Cu(0)-RDRP.

As such, the PMA was isolated and purified (Figure 2.27) prior to addition of another aliquot of MA and this resulted in a near complete shift of the initial macroinitiator peak on analysis by SEC ($Đ$ ~ 1.27 at ~ 90% conversion for the chain extension (Table 2.10, Entry 2, Figure 2.28a and 2.29)). Similar results were obtained when PMA was chain extended with butyl acrylate (BA) (Table 2.10, Entry 3, Figure 2.28b and 2.30). In addition, PMA was chain extended with styrene, furnishing a well-defined diblock poly(MA)-*b*-polystyrene copolymer with $Đ$ ~ 1.21 and $M_{n\,(SEC)}$ ~ 12200 (Table 2.10, Entry 4 and Figures 2.9 and 2.32). The same PMA macroinitiator could also

be chain extended with a larger aliquot of styrene forming higher MWt diblock copolymers of $M_{n\,(SEC)}$ = 19900 and $Đ$ ~ 1.24 (Table 2.10, Entry 5 and Figure 2.31). This is a significant achievement as it demonstrates that cross propagation is also possible in our system despite the poly(acrylates) being under not typically ideal conditions. As such, all the monomer families selected could be effectively polymerised under the universal conditions exhibiting in all cases good control over MWDs, high conversions and high end group fidelity.

Table 2.10: ^{1}H NMR and SEC analysis of the chain extension of a PMA macroinitiator with methyl acrylate, butyl acrylate and both one and two equivalent of styrene.[a]

Entry	Polymer	Target DP	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	$Đ$
1[a]	PMA	50	92	4200	5000	1.22
2[b]	P(MA-*b*-MA)	50	89	11900	10100	1.27
3[b]	P(MA-*b*-BA)	50	80	9300	10200	1.35
4[c]	P(MA-*b*-Sty)	50	81	8400	12200	1.21
5[c]	P(MA-*b*-Sty)	100	73	11800	19900	1.24

[a]In the homopolymerisation 5 cm of Cu(0) wire, 5% $CuBr_2$ and 18% PMDETA with respect to initiator were utilised and polymer purified after 6 hours. [b]Chain extension with a 1:1 ratio of monomer to solvent and 0.18 equivalents of PMDETA. [c]Chain extension with 1:1 ratio of monomer to solvent and 0.36 equivalents of PMDETA.

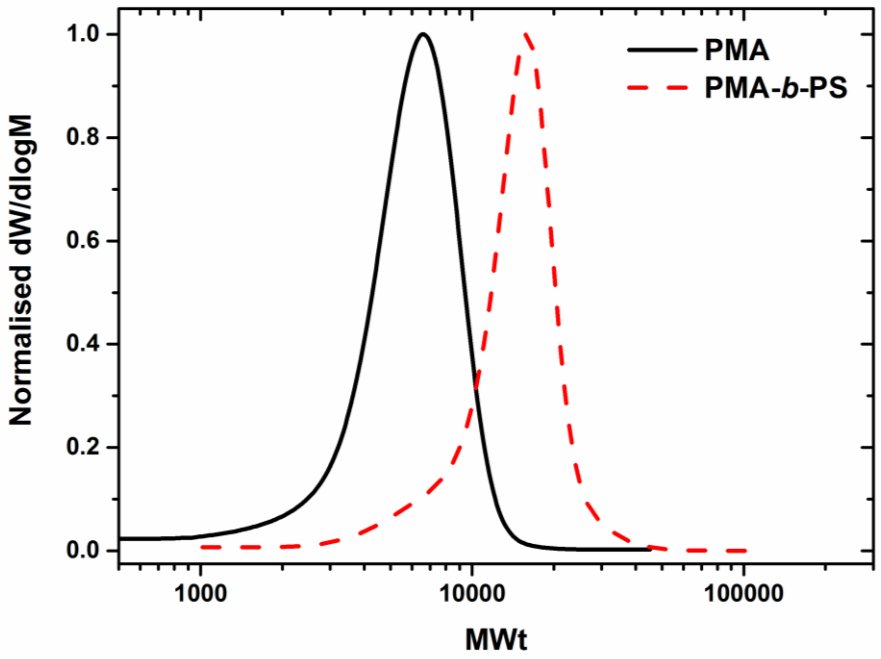
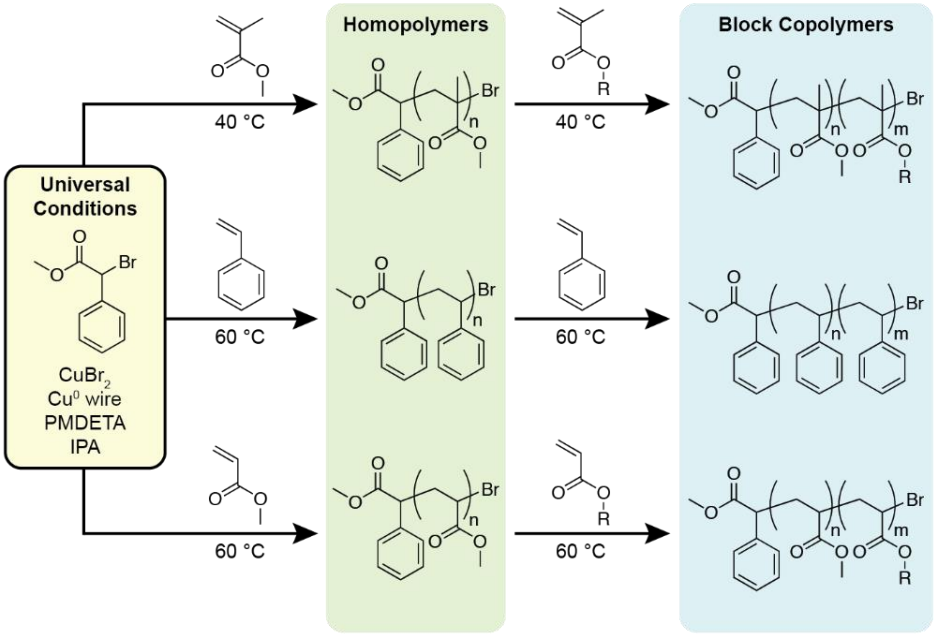


Figure 2.9: SEC analysis of the chain extension of a purified poly(methyl acrylate) macroinitiator (DP50) with styrene.

2.3. Conclusions

In this chapter the efficacious and controlled polymerisation of acrylates, methacrylates and styrene under one set of universal reaction conditions is illustrated, yielding well-defined materials with low dispersities often at near quantitative conversions. High end group fidelity was also demonstrated by successful chain extension from PMMA, PS and PMA macroinitiators generating a range of diblocks without compromising the control over the molecular weight distributions. All polymerisations utilised MBPA as the initiator, PMDETA as the ligand, IPA as the solvent, Cu(0) wire as the copper source and $CuBr_2$ as deactivator. Importantly all the materials employed are commercially available and inexpensive while the solvent used (IPA) is environmentally friendly and the Cu(0) catalyst used is in ppm levels. Employing one set of conditions (i.e. all identical components) for the controlled polymerisation of three broadly applicable monomer families while utilising readily available reagents, will allow facile access to advanced polymeric materials for all researchers.



Scheme 2.1: Universal conditions illustrating the synthesis of polyacrylate, polymethacrylate and polystyrene homo and block copolymers via Cu(0)-RDRP.

2.4. Experimental Part

2.4.1. Materials

All materials were purchased from Sigma Aldrich (Merck) or VWR and used as received unless otherwise stated. All monomers were used as received, without subsequent purification. HPLC IPA (99.9%) was used for all the experiments, including the chain extensions. *Tris*-(2-(dimethylamino)ethyl)amine (Me_6Tren) was synthesised according to previously reported literature and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) was distilled prior to use. Cu(0) (gauge 0.25 mm) wire was purchased from Comax Engineered wires and purified by immersion in conc. hydrochloric acid (HCl) for 15 minutes and subsequently rinsed with water and dried prior to use.

2.4.2. Instrumentation

^{1}H NMR spectra were recorded on Bruker DPX-300 or DPX-400 spectrometers in $CDCl_3$. Chemical shifts are given in ppm downfield from the internal standard tetramethylsilane. Monomer conversions were determined via ^{1}H NMR spectroscopy by comparing the integrals of monomeric vinyl protons to polymer signals. $M_{n\ (theory)}$ was calculated by multiplying the percentage conversion by the target molecular weight.^{13}C NMR spectra were recorded on Bruker Avance 500 MHz, equipped with a DCH ^{13}C-optimised cryoprobe. Size exclusion chromatography measurements were conducted using an Agilent 390-LC MDS instrument fitted with differential refractive index (DRI), viscometry (VS), dual angle light scattering (LS) and two wavelength UV detectors. The system was equipped with two PLgel 5 mm mixed-C columns (300 x 7.5 mm), one PLgel 5 μm guard column and autosampler. Narrow linear poly(methyl methacrylate) standards were utilised for SEC analysis of polymethacrylates and polyacrylates, and polystyrene standards were utilised for SEC analysis of PS (Agilent EasyVials, synthesised by living

anionic polymerisation) with molecular weights ranging from 200 to 1.0 x10^6 g mol^{-1} were used as calibrants. Samples were run at a flow rate of 1.0 mL min^{-1} at 30 ˚C. All samples were passed through a 0.22 μm GVHP membrane prior to analysis. The mobile phase was THF with 2% Triethylamine (TEA) and 0.01% butylated hydroxytoluene (BHT) additives. Experimental molar mass ($M_{n\ (SEC)}$) and dispersity ($Đ$) values were analysed using Agilent GPC/SEC software (version 1.2). MALDI-ToF-MS was conducted using a Bruker Daltonics Ultraflex II MALDI-ToF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. Solutions in tetrahydrofuran (50 μL) of trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propyldene] malonitrile (DCTB) or dithranol as a matrix (saturated solution), sodium iodide or silver trifluoroacetate as the cationisation agent (1.0 mg mL^{-1}) and sample (1.0 mg mL^{-1}) were mixed, and 0.7 μL of the mixture was applied to the target plate. Spectra were recorded in reflectron mode calibrated with PEG-Me 1900 kDa.

2.4.3. General Procedures

2.4.3.1. General Procedure for a Typical Cu(0)-RDRP of Methyl Methacrylate

Methyl methacrylate (4 mL or 3.76 g, 50 equiv.), pre-activated copper wire (5 cm), methyl-α-bromophenylacetate (MBPA) (0.119 mL or 0.171 g, 1 equiv.), $CuBr_2$ (8.35 mg, 0.05 equiv.) and IPA (4 mL) were added to a septum sealed vial, equipped with a stirring bar, around which the copper wire was wrapped. The mixture was subsequently deoxygenated by bubbling with nitrogen for 20 min. PMDETA (0.057 mL, 0.36 equiv.) was then introduced in the vial via a gas-tight syringe and the polymerisation was allowed to commence at 40 ˚C for 18 h. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

2.4.3.2. General Procedure for a Typical Cu(0)-RDRP of Styrene

Styrene (4 mL or 3.64 g, 50 equiv.), pre-activated copper wire (5 cm), MBPA (0.111 mL or 0.160 g, 1 equiv.), $CuBr_2$ (7.80 mg, 0.05 equiv.) and IPA (4 mL) were added to a septum sealed vial. The copper wire was wrapped around the stirrer bar and the mixture was subsequently deoxygenated by bubbling with nitrogen for 20 min. PMDETA (0.052 mL, 0.36 equiv.) was then introduced in the vial via a gas-tight syringe and the polymerisation was allowed to commence at 60 ˚C for 36 h. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

2.4.3.3. General Procedure for a Typical Cu(0)-RDRP of Methyl Acrylate

MA (4 mL or 3.82 g, 50 equiv.), pre-activated copper wire (5 cm), MBPA (0.140 mL or 0.203 g, 1 equiv.), $CuBr_2$ (9.92 mg, 0.05 equiv.) and IPA (4 mL) were added to a septum sealed vial. The copper wire was wrapped around the stirrer bar and the mixture was subsequently deoxygenated by bubbling with nitrogen for 20 min. PMDETA (0.033 mL, 0.18 equiv.) was then introduced in the vial via a gas-tight syringe and the polymerisation was allowed to commence at 60 ˚C for 12 h. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

2.4.3.4. General Procedure for a Typical Chain Extension of PMMA with MMA

The general procedure for the homopolymerisation of MMA by Cu(0)-RDRP was followed, as given above. Homopolymer conversions were monitored by regular sampling to accurately determine the time at which near quantitative monomer conversion was reached according to ^{1}H NMR ($CDCl_3$). In subsequent experiments the

homopolymerisation of MMA was allowed to proceed for 8 h, prior to the addition of a mixture of freshly deoxygenated MMA (4 mL or 3.76 grams, 50 equiv.), IPA (4 mL) and PMDETA (0.057 mL, 0.36 equiv.). The polymerisation was allowed to proceed at 40 ˚C for a further 18 h. Samples were taken under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

2.4.3.5. General Procedure for a Typical Chain Extension of PS with Styrene

The general procedure for the homopolymerisation of styrene by Cu (0)-mediated RDRP was followed as given above. Homopolymer conversions were monitored by regular sampling to accurately determine the time at which full monomer conversion was reached according to ^{1}H NMR ($CDCl_3$). In subsequent experiments the homopolymerisation of styrene was allowed to proceed for 36 h, before addition of a mixture of freshly deoxygenated styrene (8 mL or 7.28 grams, 50 equiv.), IPA (8 mL) and PMDETA (0.057 mL, 0.36 equiv.). The polymerisation was allowed to proceed for a further 36 h at 60 ˚C. Samples were taken under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

2.4.3.5. General Procedure for a Typical Chain Extension of PMA with Styrene

PMA macroinitiator was synthesised according to the homopolymerisation procedure, as given above. It was diluted in THF prior to filtration through a column of neutral alumina to remove dissolved copper salts. The polymer was isolated via precipitation in MeOH:H_2O (70% Methanol), and dried under vacuum. The degree of polymerisation of the PMA was calculated by ^{1}H NMR ($CDCl_3$). The macroinitiator (0.73 g, DP_n = 58, 1 equiv.) was subsequently added to MA (1.13 mL, target DP_n = 50), pre-activated copper wire (5 cm), $CuBr_2$ (1.40 mg, 0.05 equiv.) and IPA (1.13 mL) in a septum sealed vial.

The mixture was subsequently deoxygenated by purging with nitrogen for 15 min. PMDETA (0.0047 mL, 0.18 equiv.) was then introduced in the vial via a gas-tight syringe and the polymerisation was allowed to commence at 60 ˚C. Samples were taken under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

2.4.3.6. General procedure for a Typical Chain Extension of PMA with MA

PMA macroinitiator was synthesized according to the homopolymerization procedure, as given above. It was diluted in THF prior to filtration through a column of neutral alumina to remove dissolved copper salts. The polymer was isolated via precipitation in MeOH:H_2O (70% MeOH), and dried under vacuum. The degree of polymerization of the PMA was calculated by ^{1}H NMR ($CDCl_3$). The macroinitiator (0.73 g, DP_n = 58, 1 equiv.) was subsequently added to MA (1.13 mL, target DP_n = 50), pre-activated copper wire (5 cm), $CuBr_2$ (1.40 mg, 0.05 equiv.) and IPA (1.13 mL) in a septum sealed vial. The mixture was subsequently deoxygenated by purging with nitrogen for 15 min. PMDETA (0.0047 mL, 0.18 equiv.) was then introduced in the vial via a gas-tight syringe and the polymerization was allowed to commence at 60 ˚C. Samples were taken under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

2.5. Additional Characterisation

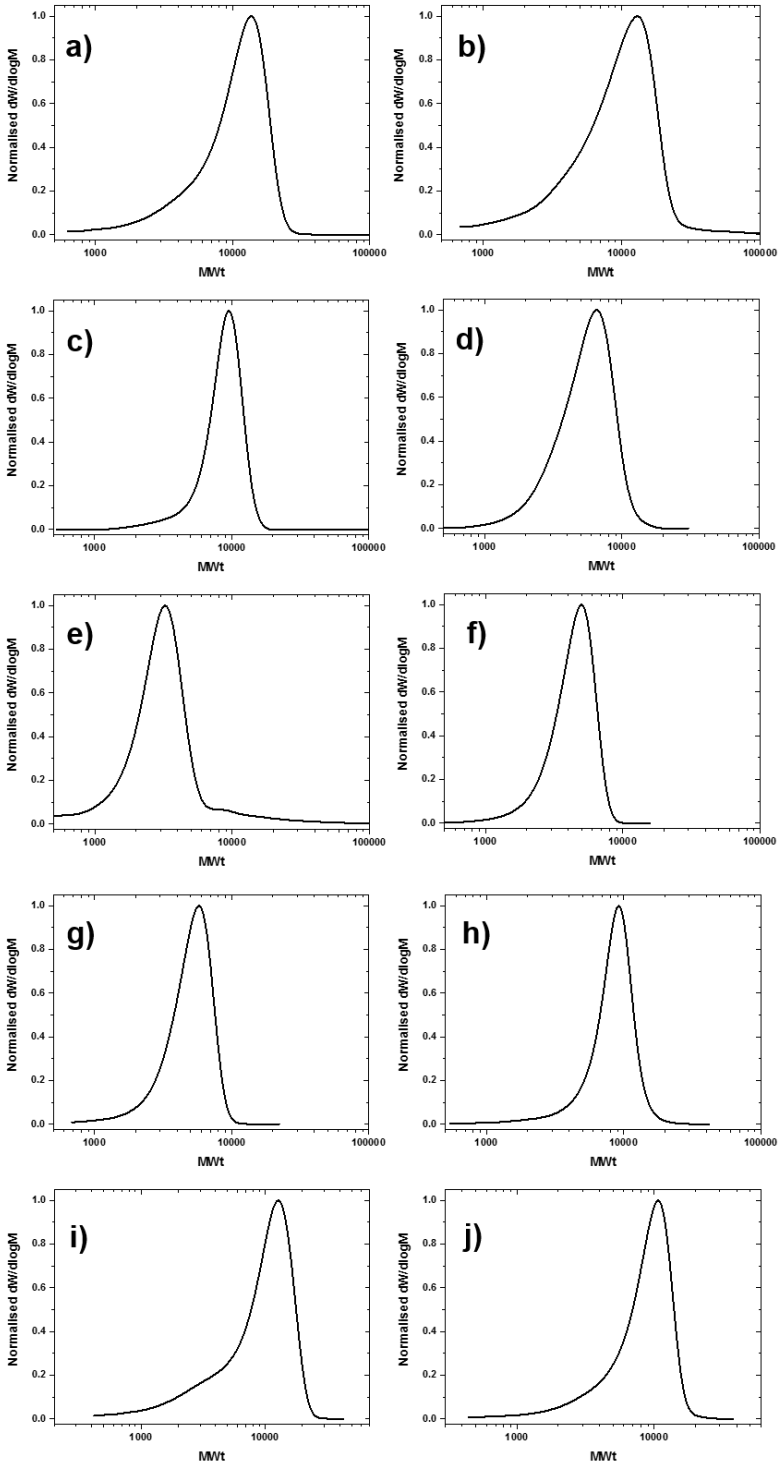


Figure 2.10: SEC analysis of poly(methyl methacrylate) prepared via Cu(0)-RDRP illustrating optimisation of solvent, ligand, temperature and ligand concentration. The figures correspond to entries in Table 2.1 with a) Entry 1 b) Entry 2 c) Entry 3 d) Entry 4 e) Entry 6 f) Entry 7 g) Entry 8 h) Entry 10 i) Entry 11 and j) Entry 12.

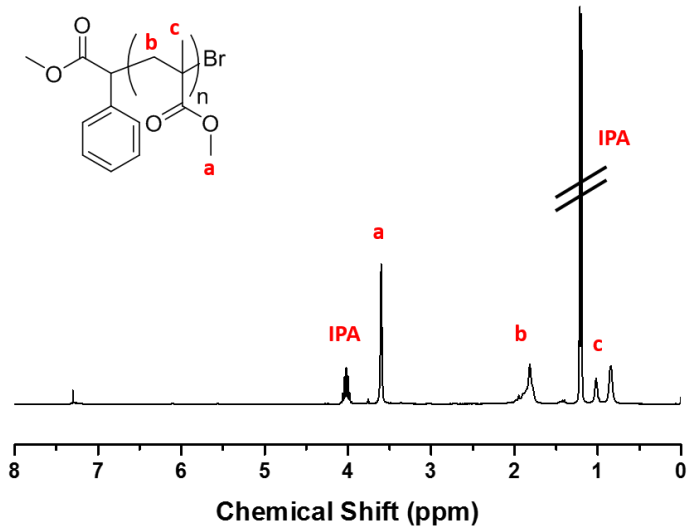


Figure 2.11: Typical crude ^{1}H NMR spectrum of PMMA in $CDCl_3$.

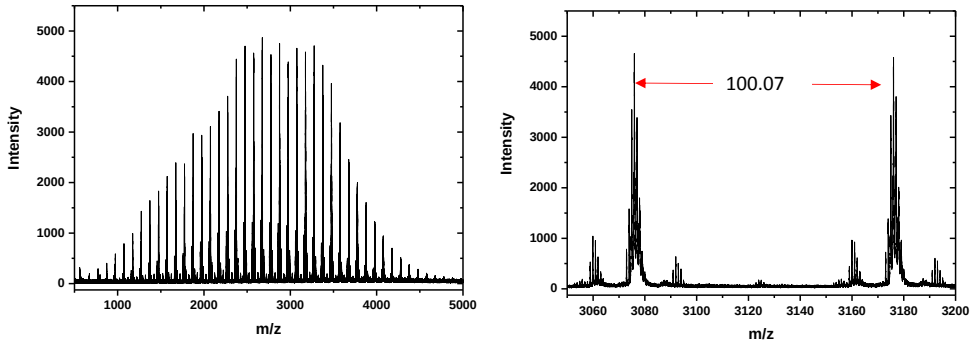


Figure 2.12: MALDI-ToF-MS spectra of PMMA synthesised via Cu(0)-RDRP. Note the peaks at an m/z of 3058, 3074 and 3090 are lithium, sodium and potassium adducts respectively.

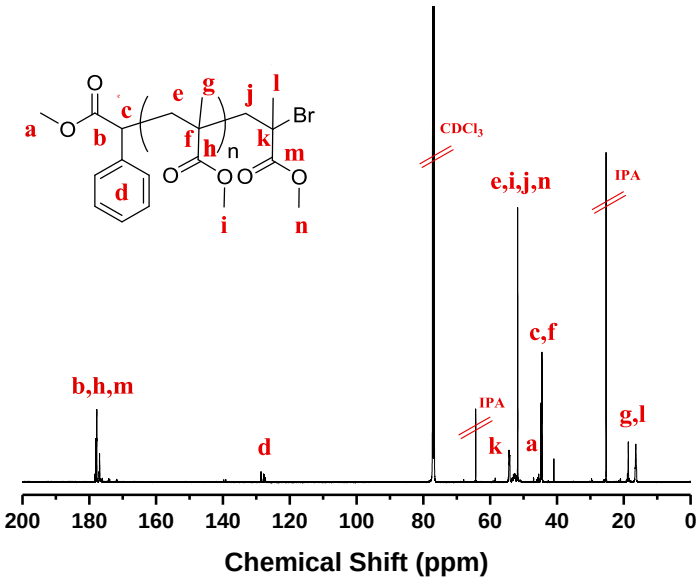


Figure 2.13: ^{13}C NMR of PMMA synthesised via Cu(0)-RDRP.

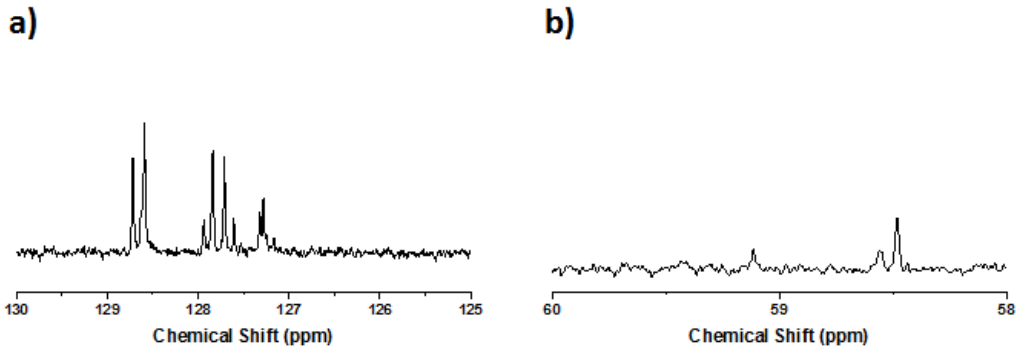


Figure 2.14: Zoomed in ^{13}C NMR of PMMA, highlighting the carbons from a) the phenyl ring from the initiator and b) polymer end group.

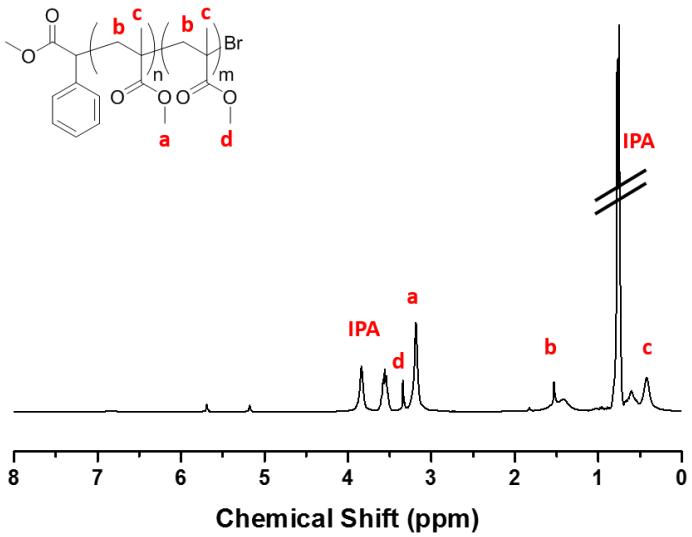


Figure 2.15: Typical crude ^{1}H NMR spectrum of P(MMA-*b*-MMA) in $CDCl_3$.

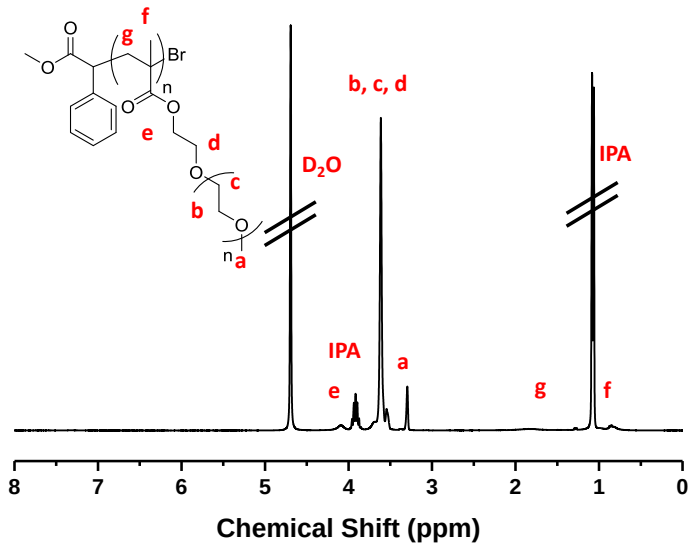


Figure 2.16 Typical crude ^{1}H NMR spectrum of P(PEGMA) in D_2O.

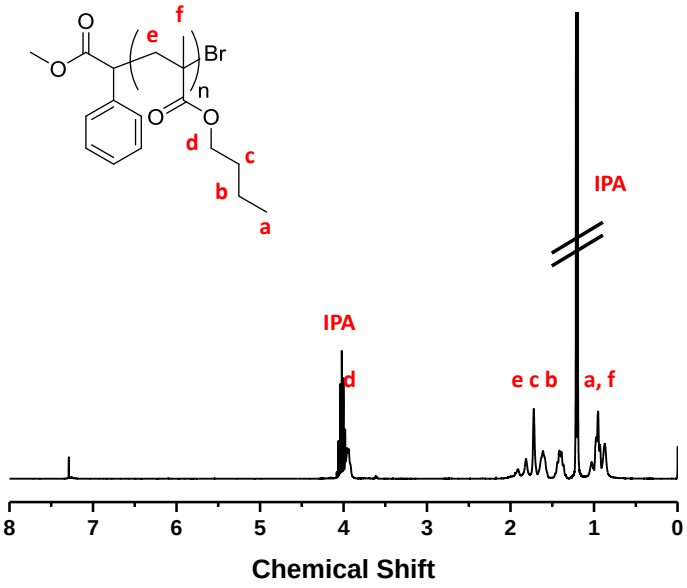


Figure 2.17: Typical crude ^{1}H NMR spectrum of PBMA in $CDCl_3$.

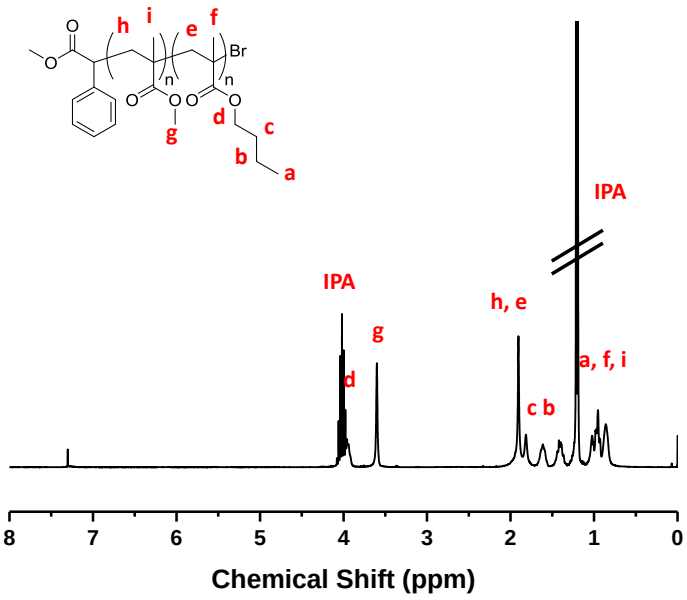


Figure 2.18: Typical crude ^{1}H NMR spectrum of P(MMA-*b*-BMA) in $CDCl_3$

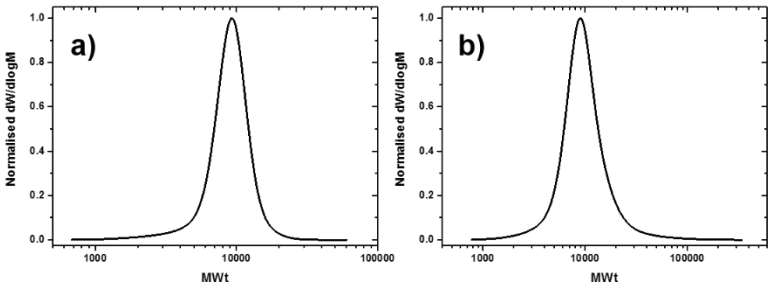


Figure 2.19: SEC analysis of polystyrene prepared via Cu(0)-RDRP illustrating optimisation of temperature and ligand concentration. The Figures correspond to entries in Table 2.5 with a) Entry 2 and b) Entry 3.

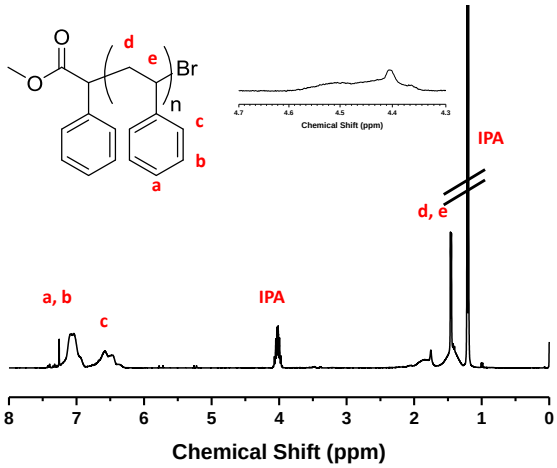


Figure 2.20: Typical crude ^{1}H NMR spectrum of PS in $CDCl_3$, illustrating the CH-Br proton (zoomed in).

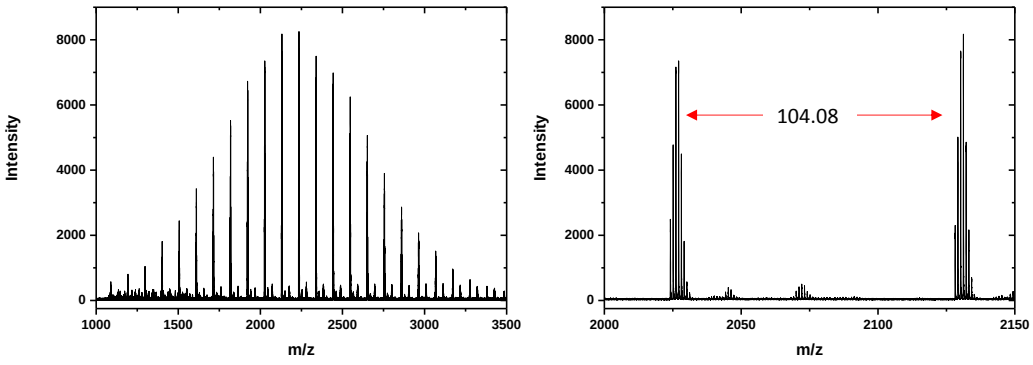


Figure 2.21: MALDI-ToF-MS spectra of polystyrene synthesised via Cu(0)-RDRP.

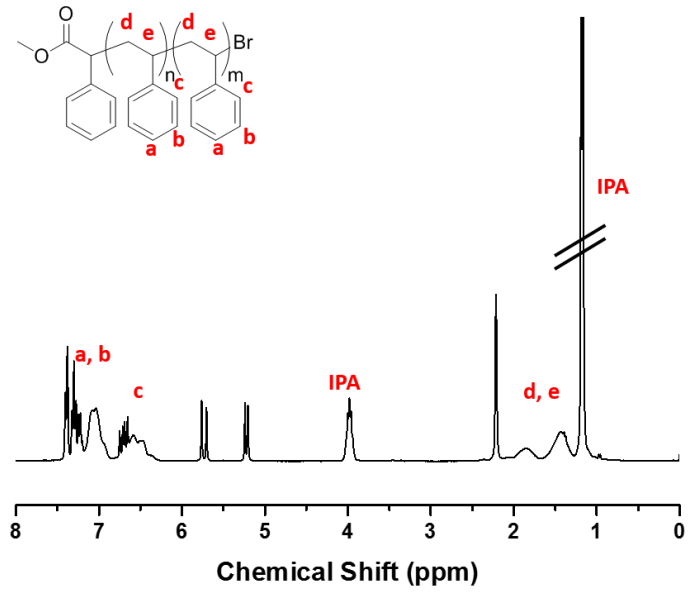


Figure 2.22: Typical crude ^{1}H NMR spectrum of P(Sty-*b*-Sty) in $CDCl_3$.

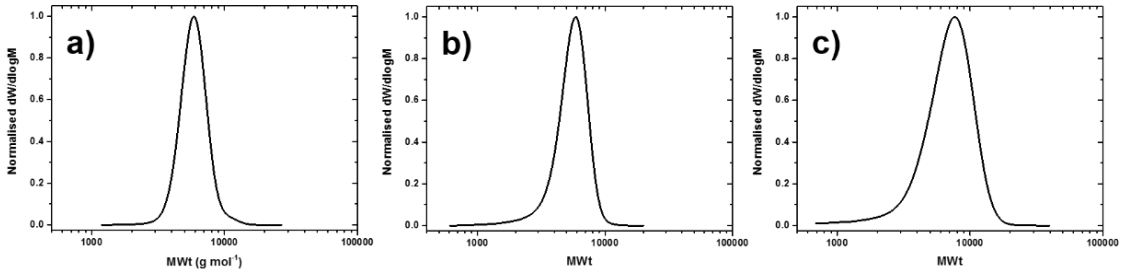


Figure 2.23: SEC analysis of poly(methyl acrylate) prepared via Cu(0)-RDRP illustrating optimisation of solvent, ligand, temperature and ligand concentration. The figures correspond to entries in Table 2.8 with a) Entry 1 b) Entry 2 and c) Entry 5.

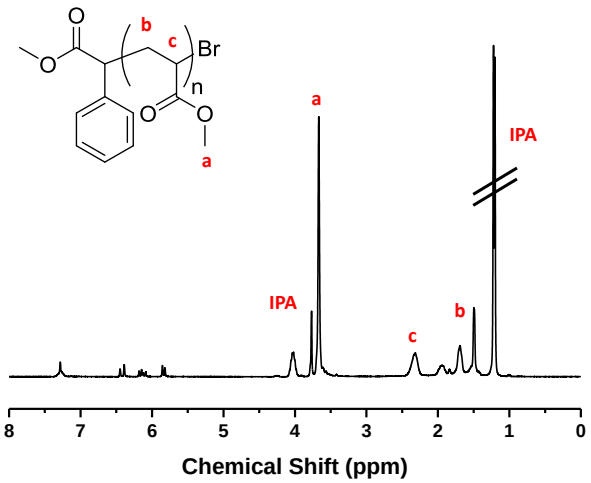


Figure 2.24: Typical crude ^{1}H NMR spectrum of PMA in $CDCl_3$.

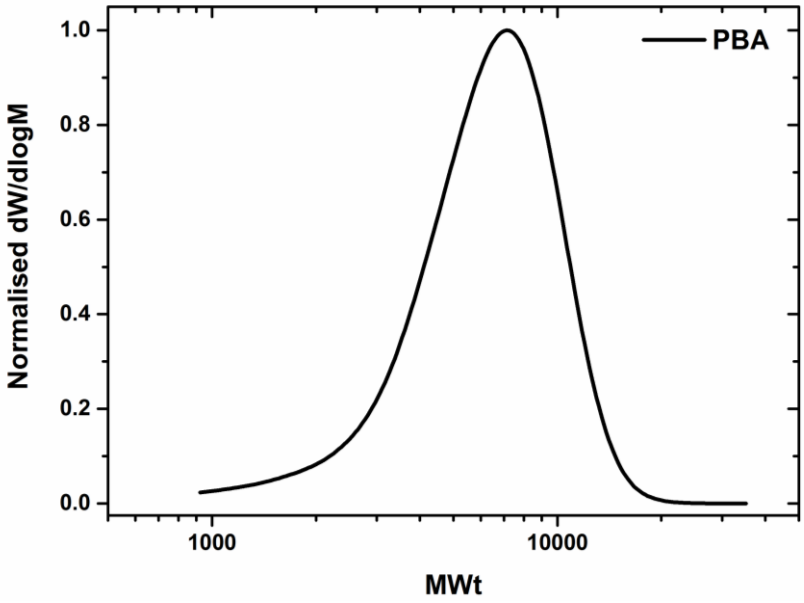


Figure 2.25 SEC analysis of poly(butyl acrylate) prepared via Cu(0)-RDRP in IPA at 60 ˚C under the following reaction conditions [MBPA]:[BA]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.18].

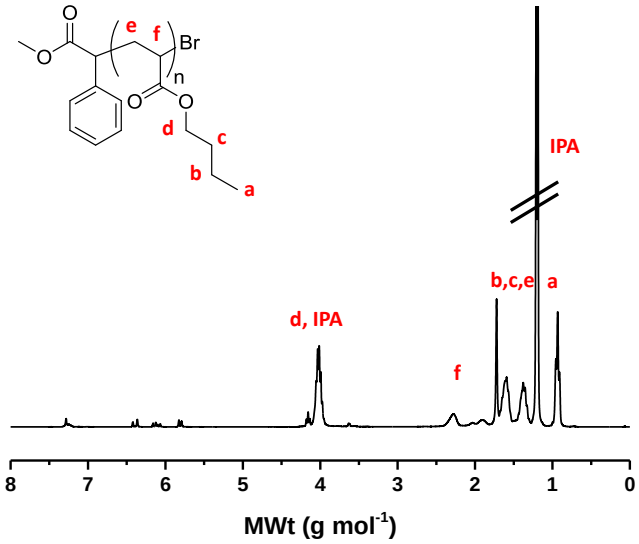


Figure 2.26: Typical crude ^{1}H NMR spectrum of PBA in $CDCl_3$.

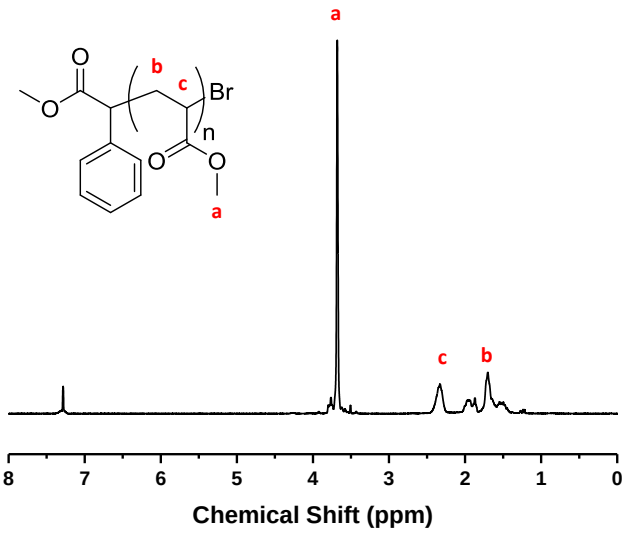


Figure 2.27: ^{1}H NMR of the purified PMA in $CDCl_3$.

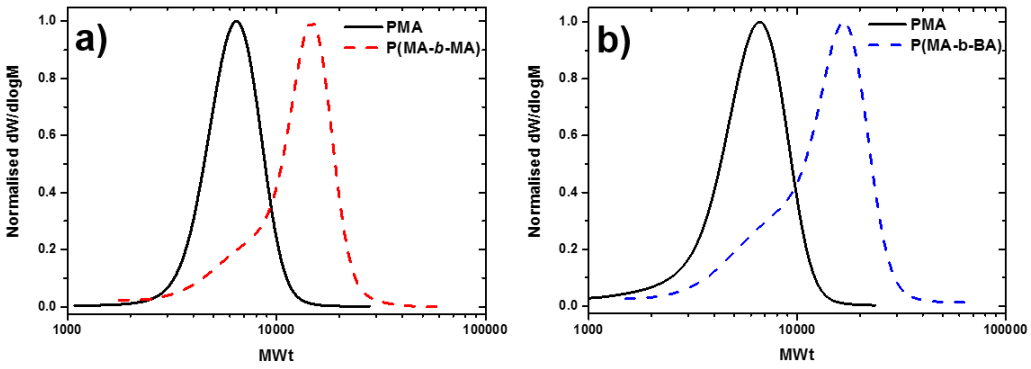


Figure 2.28: SEC analysis of the chain extension of a purified poly(methyl acrylate) macroinitiator (DP50) with a) methyl acrylate and b) butyl acrylate

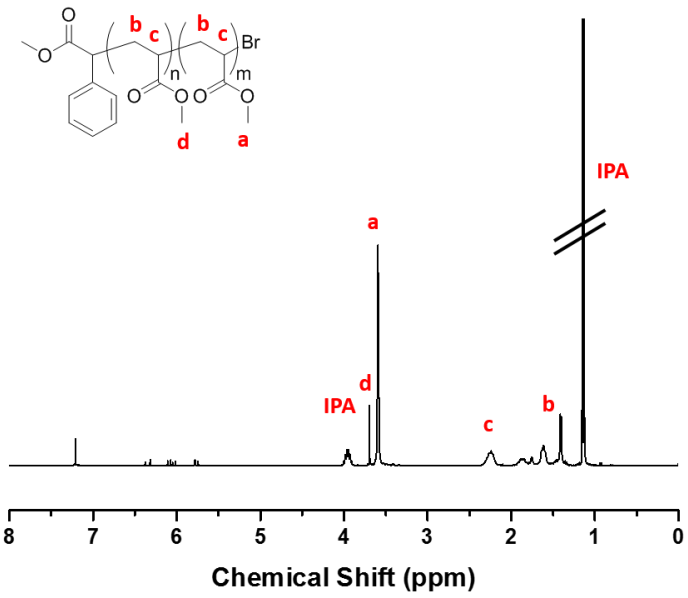


Figure 2.29: Typical crude ^{1}H NMR spectrum of P(MA-*b*-MA) in $CDCl_3$

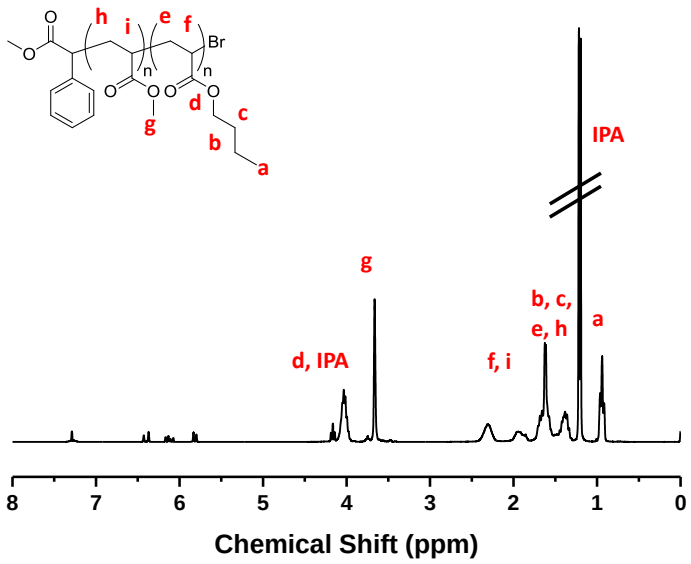


Figure 2.30: Typical crude ^{1}H NMR spectrum of P(MA-*b*-BA) in $CDCl_3$

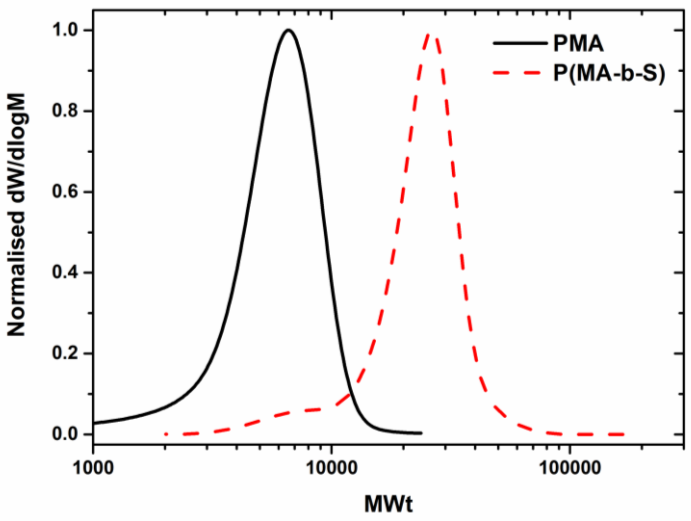


Figure 2.31: SEC analysis of the chain extension of a purified poly(methyl acrylate) macroinitiator (DP50) with styrene (DP100)

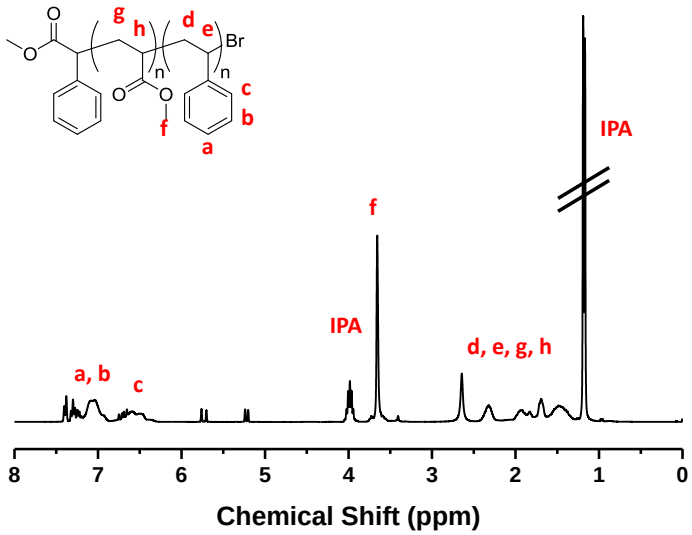


Figure 2.32: Typical crude ^{1}H NMR spectrum of P(MA-*b*-Sty) in $CDCl_3$

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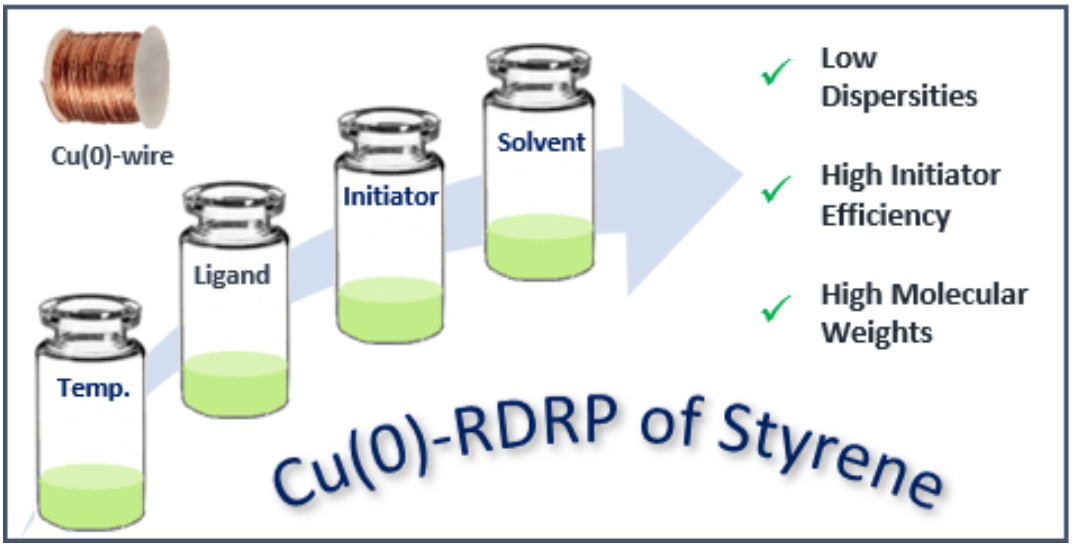
Chapter 3: Cu(0)-RDRP of styrene: Balancing initiator efficiency and dispersity



Cu(0)-RDRP is a powerful technique to synthesise a wide range of polymeric materials and architectures with controlled molecular weight, low dispersities and high end group fidelity. The vast majority of previous reports using this technique focus on the polymerisation of acrylates or methacrylates, with very limited examples on styrene, which is surprising as this is one of the most important vinyl monomers. This chapter is a comprehensive study illustrating the optimisation of conditions for the Cu(0)-wire mediated polymerisation of styrene yielding both enhanced initiator efficiency and dispersity. The structure of the ligand, the type of the initiator, the nature of the solvent and the catalyst concentration have been systematically varied to afford polystyrene at relatively high molecular weights (~ 50, 000 g mol^{-1}) with excellent agreement between theoretical and experimental number average molecular weight values and good control over the molecular weight distributions (Đ ~ 1.15).

This chapter is adapted from *Polym. Chem.*, 2018, **9**, 4395-4403

3.1. Introduction

Over the past decades reversible deactivation radical polymerisation has greatly advanced the field of controlled polymerisation. The development of RAFT[1-3] polymerisation, NMP[4, 5] and ATRP[6-8] have allowed the synthesis of complex polymeric materials with controlled architecture and molecular weight, narrow molecular weight distributions and high end group functionality.[9-13] Among these techniques, Cu(0)-wire RDRP[14-16] has attracted considerable attention as a versatile and robust methodology demonstrating broad monomer scope, yielding polymers with high end group fidelity even at near-quantitative conversions. Perhaps the most significant advantage of Cu(0)-RDRP is its simplicity[17] as the reactions can often be carried out in a disposable vial (rather than Schlenk tubes) with simple deoxygenation *via* nitrogen bubbling for a few minutes being sufficient for a controlled polymerisation, rather than time-consuming freeze-pump-thaw cycles. In addition, the majority of the Cu(0)-wire catalyst can be removed post-polymerisation by simply removing the wire and stirrer it is wrapped around. This results in a polymerisation product mixture with only ppm concentrations of copper, which can subsequently be simply removed, circumventing the perceived issues of product metal contamination and any associated residual colour.[18, 19]

To date, Cu(0)-RDRP has been extensively explored for the synthesis of polyacrylates demonstrating an impressive monomer scope, initiator, ligand and solvent choice.[14] Importantly, polyacrylates can be easily prepared over a wide range of molecular weights and architectures which is exemplified by the synthesis of high-ordered complex materials.[20-22] Whittaker, Haddleton and Junkers were the first to effectively use this technique in the preparation of high-order multiblock copolymers with unprecedented control and minimal loss of end-group fidelity.[23-27] Significantly, this methodology involves no purification between successive blocks as each step is taken to

full monomer conversion, paving the way for the design and synthesis of a new generation of materials. More recently, similar advancements have been accomplished with polyacrylamides by exploiting the rapid disproportionation (usually < 1 minute) of CuBr/Me_6Tren into Cu(0) particles and $CuBr_2$ in either aqueous or mixtures of aqueous and alcoholic media.[28-31] In contrast to monomers with relatively high k_p such as acrylates and acrylamides, monomer with lower k_p such as methacrylates are more rarely explored, due to additional problems associated with low propagation constants of this monomer class. Nevertheless, the controlled polymerisation of methacrylates *via* Cu(0)-RDRP has been reported in both aqueous and organic media with an acceptable level of control.[32-34]

Interestingly, the synthesis of polystyrene by Cu(0)-RDRP has received very little attention to date which is rather surprising given the importance of this material from both an engineering and technological standpoint.[35] Due to the low k_p of this monomer, reaction times are significantly longer and reaction temperatures typically higher in comparison to acrylate polymerisations. Perhaps the most representative report is by Perrier, Harrison and co-workers who successfully synthesised polystyrene *via* Cu(0)-RDRP with dispersity 1.2.[36] However, the maximum molecular weight attained was ~ 20000 g mol^{-1} while the catalyst employed was Cu(0)-particles which have been reported to be a less effective when compared to Cu(0)-wire.[37, 38] In addition, different types of solvents and initiators were not investigated. A few other reports demonstrate higher dispersities (Đ = 1.40-4), thus highlighting that optimal conditions for the polymerisation of styrene by Cu(0)-RDRP have yet to be found.[39, 40]

Herein this chapter illustrates a comprehensive study of the Cu(0)-RDRP of styrene utilising wire as an a more efficient Cu(0) source. A wide range of initiators, ligands and solvents are employed to identify optimal conditions and obtain well-defined polystyrene in a facile manner. The effect of these components (initiator and ligand

structures illustrated in Figure 3.1) on the control over the molecular weight distribution and the initiator efficiency will be investigated and critically discussed.

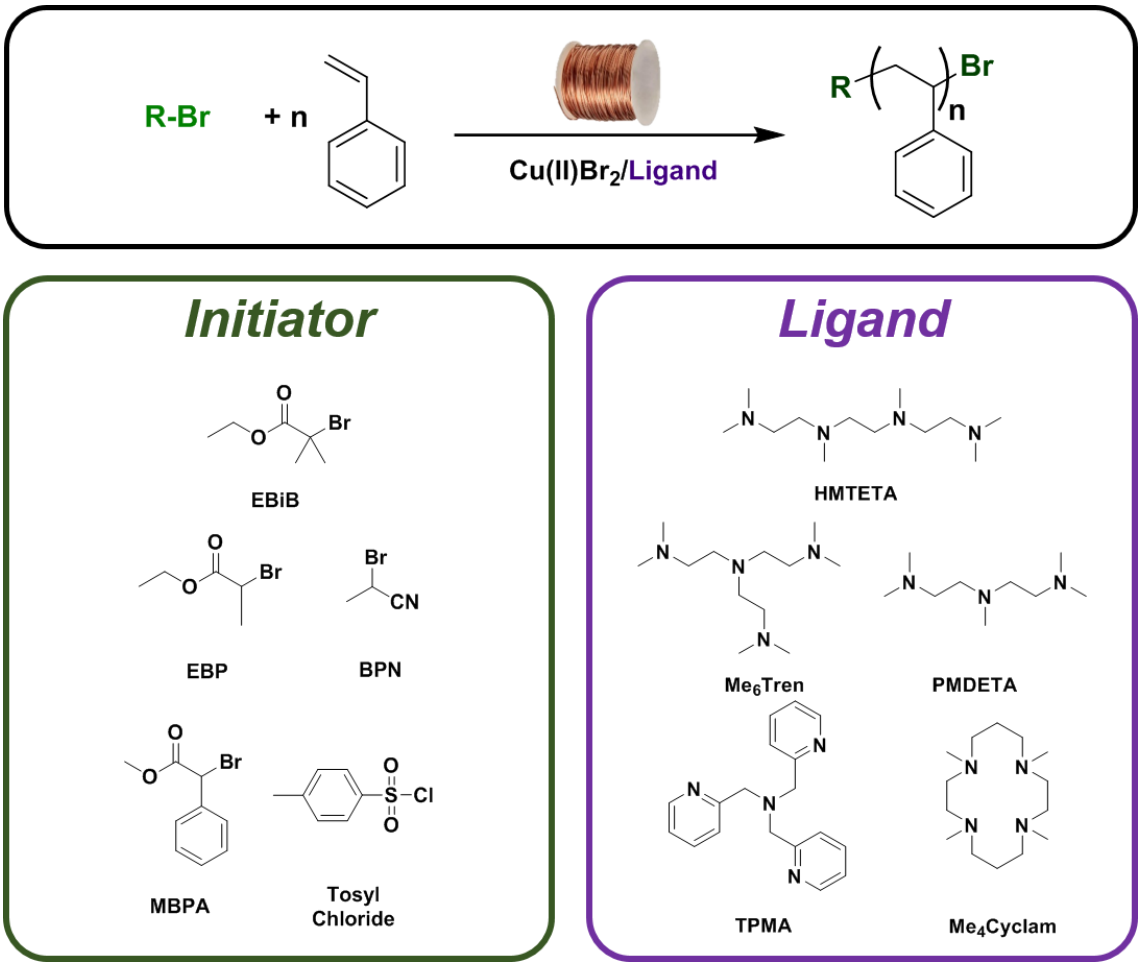


Figure 3.1: A schematic representation of the Cu(0)-wire RDRP of styrene, illustrating the structures of initiators and ligands utilised in the optimisation.

3.2 Results and Discussion

3.2.1. The Effect of Temperature

In Chapter 2, we illustrated one set of conditions to synthesise well-defined polymethacrylates, polyacrylates and polystyrene *via* Cu(0)-RDRP.[42] Although this system is ideal to provide *universal conditions* for three different monomer classes and allows for simplicity in terms of procedure for non-experts, several compromises were sought for each individual monomer class. Indeed, ideal conditions for a specific monomer class (e.g. acrylates) would not be ideal for the polymerisation of a different monomer class (e.g. styrene), particularly when high molecular weights or high initiator efficiencies are required. For acrylates and methacrylates to some extent, very well-optimised conditions *via* Cu(0)-RDRP are well reported and established.[14] On the other hand, the polymerisation of styrene *via* Cu(0)-RDRP remains poorly explored.

In the reported universal procedure and upon targeting a degree of polymerisation of 50, methyl-α-bromophenylacetate was used as the initiator, PMDETA as the ligand and isopropanol as the solvent while the ideal temperature was illustrated to be 60 °C.[42] Interestingly, at lower temperatures (25-50 °C) much slower polymerisation rates were observed with the final conversion never exceeding 70% after 36 hours of reaction time (Table 3.1, Entries 1-6 and Figures 3.2 and 3.20). However, upon increasing the temperature to 60 °C, very high conversions could be obtained (~ 98%) without compromising the control over the molecular weight distributions (Đ ~ 1.15) (Table 3.1, Entries 7-8 and Figures 3.2 and 3.21). When further increasing the temperature to 70 °C a gradual broadening of the molecular weight distribution was evident (Đ ~ 1.25) with the final dispersity greater than 1.4 when 80 °C was employed (Table 3.1, Entries 9-12 and Figures 3.2 and 3.22). This is rather surprising as traditional ATRP of styrene typically operates well at higher temperatures but in more hydrophobic solvents (for

example toluene) and as such the higher dispersities could be attributed to the use of isopropanol in combination with these elevated temperatures. Temperature can also have a significant effect in determining the relative stability and solubility of Cu(I) and Cu(II) species, which could also have an effect on the control over the polymerisation.[43, 44]

Table 3.1: ^{1}H NMR and SEC analysis of the polymerisation of styrene, with optimisation of temperature illustrated.[a]

Entry	Temp. (°C)	Reaction Time (h)	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	Đ
1	25	18	<10	-	-	-
2	25	36	31	1800	1900	1.22
3	40	18	21	1300	1400	1.19
4	40	36	67	3700	4300	1.19
5	50	18	35	2000	2400	1.13
6	50	36	73	4000	4900	1.14
7	60	18	47	2600	3800	1.14
8	60	36	98	5300	8100	1.15
9	70	18	55	3100	5200	1.17
10	70	36	>99	5600	8200	1.25
11	80	18	61	3500	6800	1.30
12	80	36	>99	5600	7800	1.42

[a]In homopolymerisations 5 cm of Cu(0) wire, 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. The volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated *via* ^{1}H NMR.

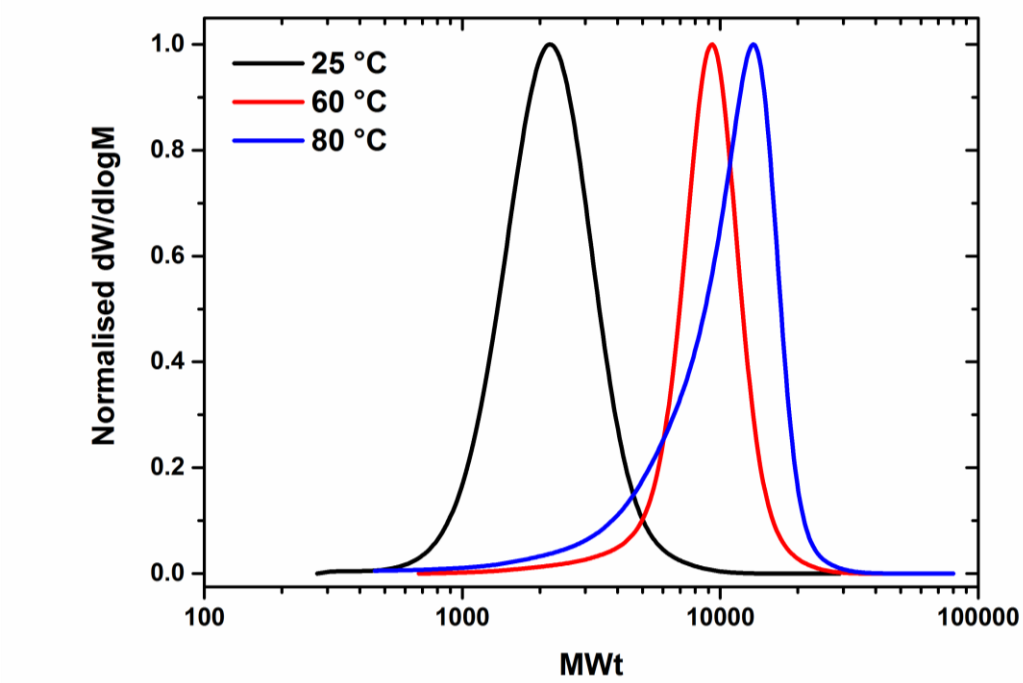


Figure 3.2: SEC chromatograms illustrating the effect of temperature on the polymerisation of styrene (Target DP50) with traces of the polymers synthesised at 25 °C, 60 °C and 80 °C respectively.

Nevertheless, even at 60 °C, very low initiator efficiency (initiator efficiency was calculated based on the ratio between the theoretical and actual molecular weight by SEC) was observed (I_{eff} = 64%) which demonstrates that these universal conditions, although sufficient when low dispersities are required, were not ideal in achieving a molecular weight close to that predicted during the polymerisation of styrene. This deviation in initiator efficiency is even more pronounced when higher targeted degrees of polymerisations were attempted. For example, when targeting DP800 (83500 g mol^{-1} molecular weight) even lower initiator efficiency was evident (I_{eff} ~ 54%) resulting in polystyrene with a molecular weight of 34300 (M_n theoretical 18500 g mol^{-1}, Table 3.3, Entry 1 and Figure 3.3). Still, however, under these conditions well-defined polystyrene of relatively high molecular weight can be obtained with a dispersity as low as 1.2.

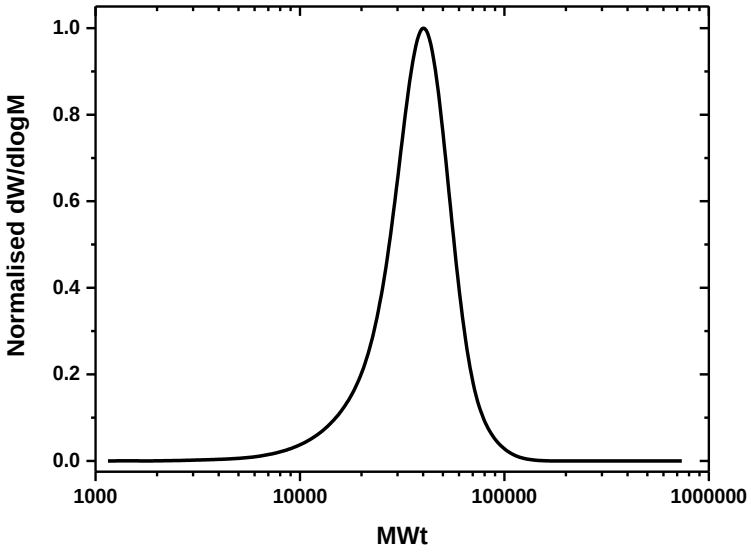


Figure 3.3: SEC analysis of polystyrene (Target DP800) prepared at 60 °C via Cu(0)-RDRP in IPA utilising MBPA at the initiator, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.36].

3.2.2. The Effect of Type and Concentration of Ligand

In our previous investigation, the concentration of PMDETA was kept constant at 0.36 equivalents with respect to the initiator. Upon systematically varying the concentration of PMDETA from 0.18 to 0.72 equivalents, no change in the molecular weight distribution was observed with low dispersities being maintained for all polymerisations (Đ ~ 1.2, Table 3.2, Entries 1-4 and Figure 3.4a). However, the initiator efficiency was significantly enhanced at higher ligand loading (0.72 equivalents).

Table 3.2: ^{1}H NMR and SEC analysis of polystyrene with target DP50 prepared via Cu(0)-RDRP in IPA, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[L]=[1]:[50]:[0.05]:[X], where the ligand [PMDETA] was varied between 0.18 and 0.72 equivalents and Me_6Ttren was varied between 0.18 and 0.54 with respect to initiator.[a]

Entry	Ligand	[L] w.r.t [I]	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	Đ
1	PMDETA	18%	66	3600	5100	1.13
2	PMDETA	36%	98	5300	8100	1.15
3	PMDETA	54%	94	5100	7000	1.19
4	PMDETA	72%	90	4900	6900	1.23
5	Me_6Tren	18%	31	1800	2100	1.12
6	Me_6Tren	36%	70	3800	7700	1.35
7	Me_6Tren	54%	67	3700	10400	3.31

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ with respect to initiator were utilised and samples were taken after 36 hours. The volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated *via* ^{1}H NMR.

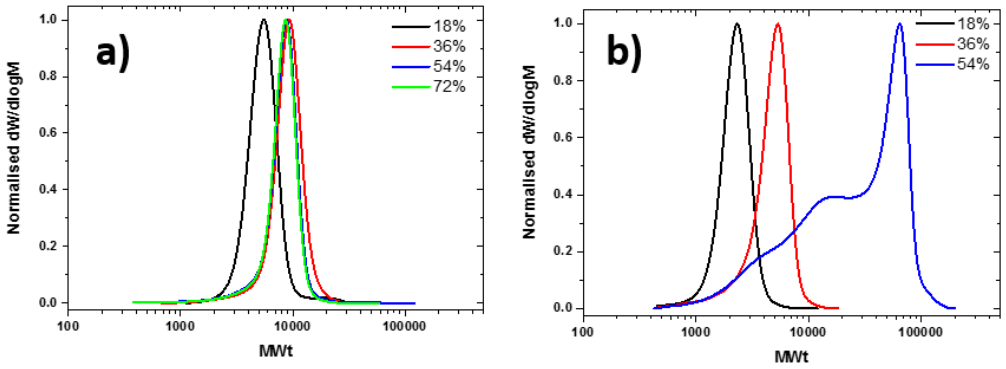


Figure 3.4: SEC chromatograms illustrating the effect of ligand concentration on the polymerisation of styrene (Target DP50) with a) PMDETA and b) Me_6Tren via Cu(0)-RDRP.

To better visualise this we targeted a higher degree of polymerisation (DP800) where the initiator efficiency was as high as 91%. (Table 3.3, Entry 2 and Figure 3.5). This is in stark contrast to when only 0.36 equivalents were utilised, where only 54% initiator efficiency was observed. This dramatic increase in efficiency with increased PMDETA concentration can be attributed to better solubility and complexation of $CuBr_2$ when more ligand is present in solution.

Table 3.3: ^{1}H NMR and SEC analysis of the polymerisation of styrene, with ligands and ligand concentrations illustrated.[a]

Entry	Ligand	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	I_{eff} (%)	Đ
1	PMDETA (36%)	22	18500	34300	54	1.22
2	PMDETA (72%)	32	26700	29200	91	1.20
3	HMTETA (36%)	28	23600	29400	80	1.29

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 800 and conversion was calculated *via* ^{1}H NMR.

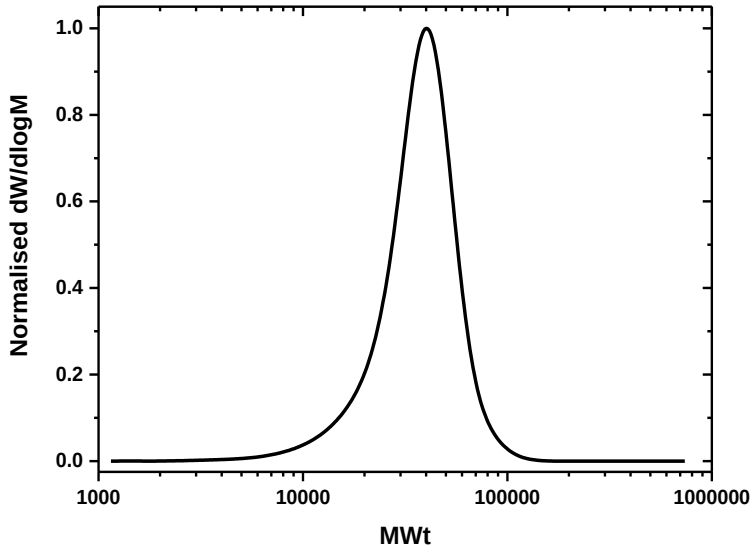


Figure 3.5: SEC analysis of polystyrene (Target DP800) prepared at 60 °C via Cu(0)-RDRP in IPA under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.72].

In an attempt to improve initiator efficiency in an alternative way, a number of ligands were subsequently screened. Me_6Tren one of the highest activity ligands reported, exhibited a relatively controlled polymerisation at 0.36 equiv. (Đ = 1.35) although complete loss of control was observed at higher concentrations (Đ ~ 3, Table 3.2, Entries 5-7 and Figure 3.4b). In contrast, at lower concentrations (0.18 equivalents) a low dispersity of 1.12 could be obtained although a significantly lower polymerisation rate was evident as opposed to PMDETA. These results suggest that when Me_6Tren is employed, lower concentrations are preferred and the controlled polymerisation of styrene to yield higher conversions is not possible with this ligand under the conditions

studied. It is also worthy of note that unusually the polymerisation with the higher activity Me_6Tren yields lower conversion in comparison to PMDETA. This is attributed to the persistent radical effect, with the higher activity ligand resulting in a higher concentration of radicals and hence termination events in the early stages of the polymerisation (this is closely linked to the low initiator efficiency). Each termination event results in the formation of a Cu(II)Br_2 molecule, so this increase in deactivator concentration results in this lower rate of polymerisation.

Table 3.4: ^{1}H NMR and SEC analysis of polystyrene with target DP50 prepared via Cu(0)-RDRP in IPA, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[Tren]=[1]:[50]:[0.05]:[X], where [Tren] was 0.18 or 0.36 equivalents with respect to initiator.[a]

Entry	[Tren] w.r.t [I]	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	Đ
1	18%	73	3900	6100	1.38
2	36%	98	5300	13500	1.64

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated *via* ^{1}H NMR.

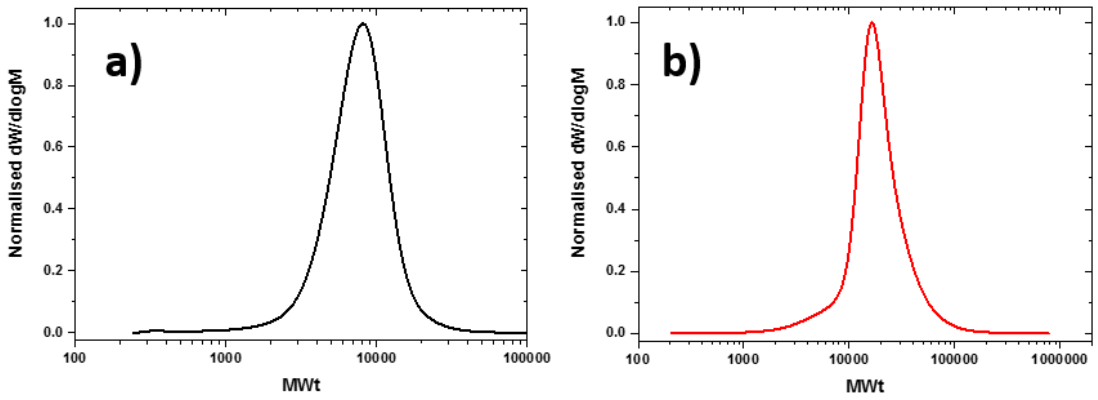


Figure 3.6: SEC analysis of polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in IPA where Tren a) 18% and b) 36% was utilised as the ligand.

A similar behaviour was observed when tris(2-aminoethyl)amine (Tren) was instead employed with an even more pronounced loss of control (Table 3.4, Entries 1-2 and Figure 3.6). A range of other ligands were also explored including bipyridine, tris(2-pyridylmethyl)amine (TPMA), 1, 4, 8, 11-tetraazacyclotetradecane (Cyclam) and Me_4-Cyclam. However, in all cases this resulted in an absence of polymerisation or a

significant loss of control, highlighting the incompatibility of these ligands to mediate the controlled polymerisation of styrene under the selected conditions (Table 3.12 and Figure 3.23).

Table 3.5: ^{1}H NMR and SEC analysis of polystyrene with target DP50 prepared via Cu(0)-RDRP in IPA, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[HMTETA]=[1]:[50]:[0.05]:[X], where [HMTETA] was 0.18 or 0.36 equivalents with respect to initiator.[a]

Entry	[HMTETA] w.r.t [I]	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	Đ
1	18%	45	2600	3200	1.16
2	36%	92	5000	8000	1.19

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated *via* ^{1}H NMR.

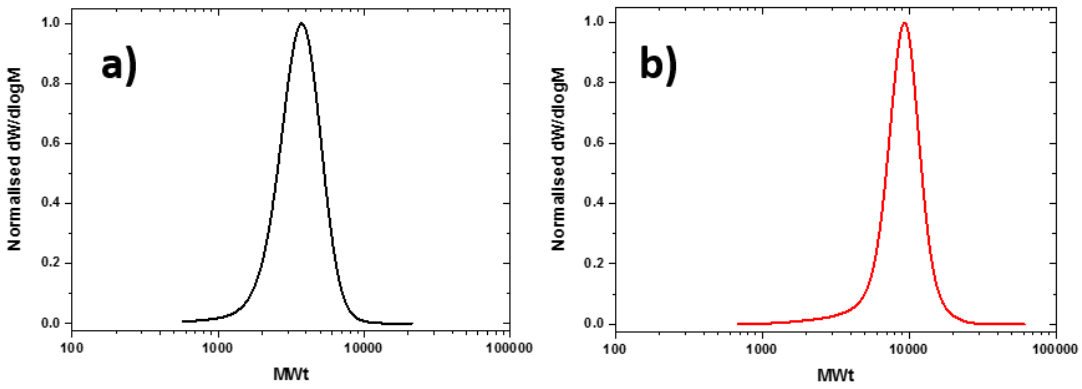


Figure 3.7: SEC analysis of polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in IPA with HMTETA a) 18% and b) 36% utilised as the ligand.

In contrast, 1, 1, 4, 7, 10, 10-hexamethyltriethylenetetramine (HMTETA) generated much higher conversions while maintaining low dispersity values (Đ < 1.20) (Table 3.5 and Figure 3.7). To further investigate whether HMTETA is a better alternative, we pushed the system further by targeting DP800. This led to well-defined polystyrene with improved initiator efficiency (I_{eff} = 80%) although broader molecular weight distributions (~ 1.29) were also observed (Table 3.3, Entry 3 and Figure 3.8). The enhanced initiator efficiency could be due to the better solubility and complexation of $CuBr_2$ with HMTETA which gave more efficient deactivation. Overall, we have shown that in IPA the initiator efficiency can be significantly improved from ~ 50 to 80-90% by

simply increasing the ligand concentration or by employing HMTETA. However, PMDETA might be a better choice since it strikes a better balance between the highest molecular weight, dispersity and initiator efficiency.

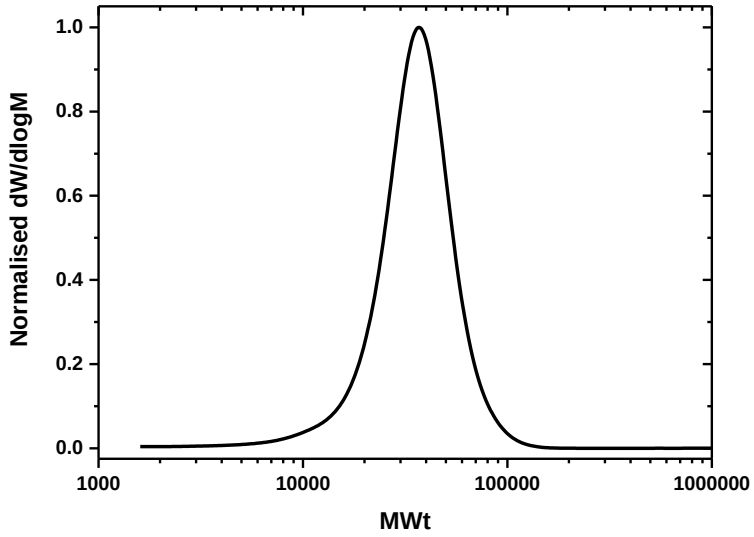


Figure 3.8: SEC analysis of polystyrene (Target DP800) prepared at 60 °C via Cu(0)-RDRP in IPA under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[HMTETA]=[1]:[800]:[0.05]:[0.36].

3.2.3. The Effect of the Initiator

In the previous section, we concluded that PMDETA allows for the preparation of well-defined polystyrene. To explore different ways to improve the initiator efficiency, we also performed an initiator study by maintaining the ligand concentration at 0.36 equivalents with respect to the initiator. The temperature was maintained at 60 °C, as previously concluded. Interestingly, when ethyl-α-bromoisobutyrate was employed no polymerisation was detected even when the reaction was left to proceed for one week (Table 3.6, Entry 1). This is surprising since conventional ATRP conditions with CuBr often successfully employing this initiator.[36, 44] This is another example which highlights the difference in behaviour of high and low ppm copper systems. When tosyl chloride was used as the initiator, in combination with $CuBr_2$ or $CuCl_2$ deactivator very poor initiator efficiency was observed (I_{eff} < 50%) (Table 3.6, Entries 5 and 6 and Figure 3.24).

This is possibly attributed to the reaction of tosyl chloride with isopropanol forming isopropyl tosylate, so this initiator was no longer explored. Impressively, however, upon employing either ethyl-2-bromopropionate (EBP) or 2-bromopropiontrile (BPN) the initiator efficiency was significantly enhanced (I_{eff} = 80%) while narrow molecular weight distributions could also be achieved (~1.10) (Table 3.6, Entries 3 and 4 and Figure 3.9). These results together demonstrate that secondary radical forming initiators (except phenylacetate which has extra stabilisation) are much more advantageous for the controlled polymerisation of styrene *via* Cu(0)-RDRP when compared to tertiary forming radical initiators. These results are attributed to a greater efficiency in the formation of secondary radicals, with isobutyrate and phenylacetate radicals resulting in the slow addition of some radicals to styrene, and subsequently termination and a reduced number of chains.

Table 3.6: ^{1}H NMR and SEC analysis of the polymerisation of styrene, with optimisation of a range of initiators shown.[a]

Entry	Initiator	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	I_{eff} (%)	$Đ$
1	EBiB	0	-	-	-	-
2	MBPA	98	5300	8100	65	1.15
3	EBP	77	4200	5300	79	1.11
4	2-BPN	77	4200	5400	78	1.10
5	Tosyl Chloride ($CuBr_2$)	66	3600	7600	47	1.26
6	Tosyl Chloride ($CuCl_2$)	67	3700	8200	45	1.29

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated *via* ^{1}H NMR.

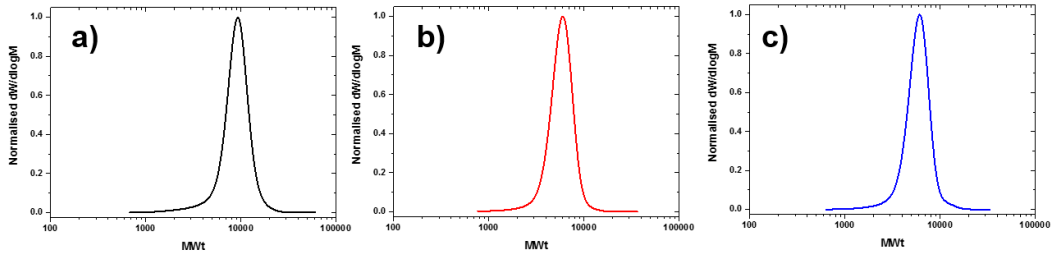


Figure 3.9: SEC chromatograms of polystyrene homopolymers (Target DP50) with narrow molecular weight distributions synthesised with our optimal initiators, a) MBPA, b) EBP and c) BPN.

Table 3.7: ^{1}H NMR and SEC analysis of polystyrene with target DP800 prepared via Cu(0)-RDRP in IPA, under the following reaction conditions [I]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.36], where [I] represents MBPA, EBP or BPN.[a]

Entry	Initiator	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	I_{eff} (%)	Đ
1	MBPA	22	18500	34300	54	1.22
2	EBP	33	27700	38500	72	1.29
3	BPN	27	22700	29600	76	1.32

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 800 and conversion was calculated *via* ^{1}H NMR.

To further probe the potential of these initiators to improve the initiator efficiency we targeted polystyrene of DP800. In agreement with our previous observations, BPN showed I_{eff} = 76% and EBP showed I_{eff} = 72%. Therefore, both initiators exhibited higher initiator efficiency as opposed to MBPA (I_{eff} = 54%) (Table 3.7, Entries 1-3 and Figure 3.10). MBPA's low initiator efficiency is related to the slow addition of some radicals to styrene resulting in termination and a lower number of polymer chains.

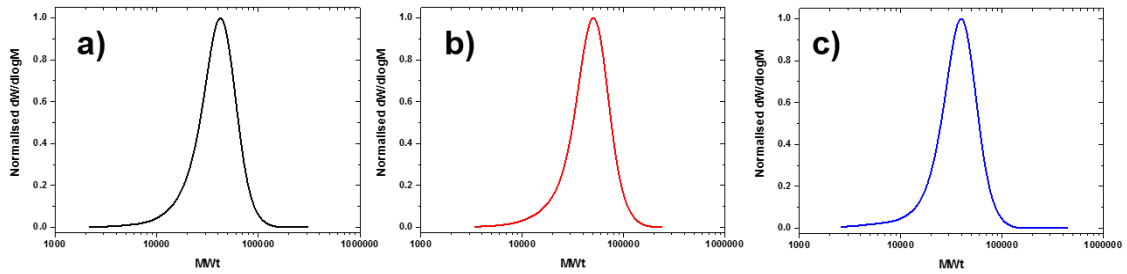


Figure 3.10: SEC analysis of polystyrene (Target DP800) prepared at 60 °C via Cu(0)-RDRP in IPA under the following reaction conditions [I]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.36], with a) MBPA, b) EBP and c) BPN as the initiator.

3.2.4. The Effect of the Solvent

To expand the scope of this system we also explored the potential of other solvents to mediate the controlled polymerisation of styrene. Polar solvents such as DMSO, DMF and ethanol (Table 3.8, Entries 1-3 and Figure 3.25) yielded uncontrolled polymerisation and polystyrene with broad molecular weight distributions while acetone, methanol and trifluoroethanol resulted in no polymerisation (Table 3.8, Entries 4-6). Methanol is likely to be reactive with certain alkyl halide compounds, which could possibly be the reason for the absence of polymerisation. However, upon using the slightly less hydrophilic alcohol tert-butanol a controlled polymerisation took place although the initiator efficiency was comparable to IPA (Table 3.8, Entries 7-8 and Figure 3.11). This could be attributed to the fact these solvents both form *biphasic* mixtures during polymerisation.[9, 45]

Table 3.8: ^{1}H NMR and SEC analysis of the polymerisation of styrene, with optimisation of solvent shown.[a]

Entry	Solvent	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	I_{eff} (%)	Đ
1	DMSO	74	4100	5500	74	1.57
2	DMF	79	4300	8000	53	1.48
3	Ethanol	75	4100	6200	66	1.58
4	Acetone	-	-	-	-	-
5	Methanol	0	-	-	-	-
6	TFE	-	-	-	-	-
7	IPA	98	5300	8100	65	1.15
8	tBuOH	96	5100	6500	78	1.23
9	Toluene	90	4800	5600	86	1.12
10	Acetonitrile	65	3600	4200	86	1.24
11	Dioxane	77	4300	4400	98	1.10
12	IPA:Tol 1:1	90	4800	7600	63	1.18
13	IPA:Tol 1:4	89	4700	7500	63	1.15

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated *via* ^{1}H NMR.

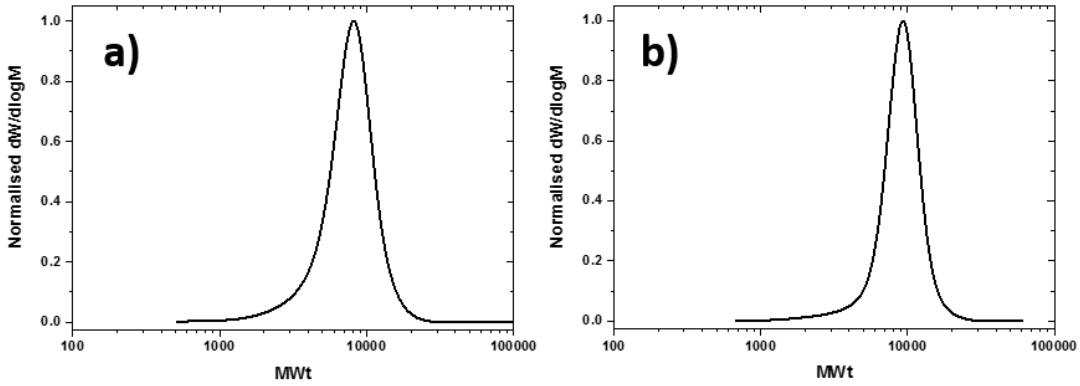


Figure 3.11: SEC analysis of polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in a biphasic system in a) tBuOH b) IPA under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.36].

Finally, toluene, acetonitrile and dioxane, were also explored (Table 3.8 Entries 9-11 and Figure 3.12). Interestingly, all three solvents were compatible with the controlled polymerisation of styrene and demonstrated improved initiator efficiencies (I_{eff} > 85% in all cases).

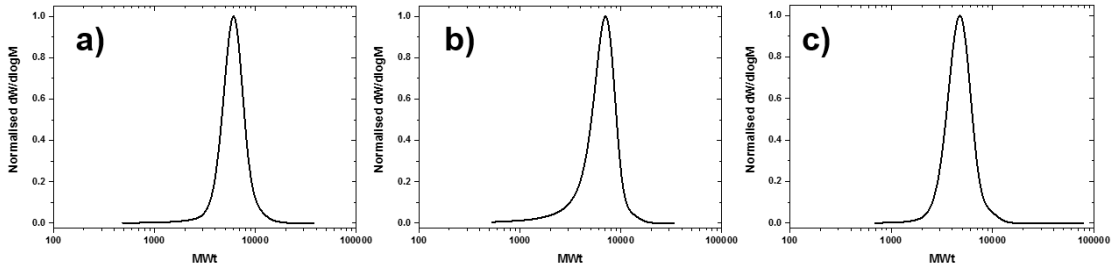


Figure 3.12: SEC analysis of well-defined polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in a) toluene b) acetonitrile and c) dioxane under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.36].

As with other optimised conditions, these three solvents were subsequently tested upon targeting polystyrene with DP800 (Table 3.9, Figure 3.13). Surprisingly, the polymerisation in acetonitrile resulted in loss of control (dispersity ~ 2) while the polymerisation in dioxane and toluene both demonstrated improved initiator efficiencies over IPA (I_{eff} = 80% and I_{eff} = 68% respectively in comparison to I_{eff} = 54%), thus highlighting the superiority of these solvents. The loss of control observed when higher molecular weights were targeted in acetonitrile, could be due to the greater ability of this solvent to in the case of acetonitrile might be due to the better stabilisation of CuBr

species relative to the deactivating Cu(II)Br_2 species. This in this solvent which may lead to faster polymerisation rates and subsequent loss of control.[46]

Table 3.9: ^{1}H NMR and SEC analysis of polystyrene with target DP800 prepared via Cu(0)-RDRP in a) toluene b) acetonitrile and c) dioxane under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.36].[a]

Entry	Solvent	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	I_{eff} (%)	Đ
1	Toluene	37	31000	45500	68	1.24
2	Acetonitrile	28	23600	64900	36	2.06
3	Dioxane	28	23600	29300	80	1.19

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 800 and conversion was calculated *via* ^{1}H NMR.

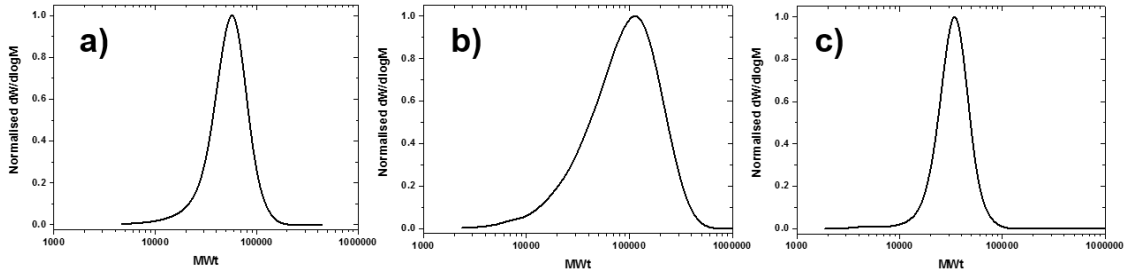


Figure 3.13: SEC analysis of well-defined polystyrene (Target DP800) prepared at 60 °C via Cu(0)-RDRP in a) toluene b) acetonitrile and c) dioxane under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.36].

Interestingly, even the addition of small amounts of IPA to a toluene polymerisation resulted in a dramatic decrease of the initiator efficiency, similar to that of IPA, thus suggesting that if high initiator efficiency is required for a styrene polymerisation, isopropanol should be avoided (Table 3.8, Entries 12-13 and Figure 3.14).

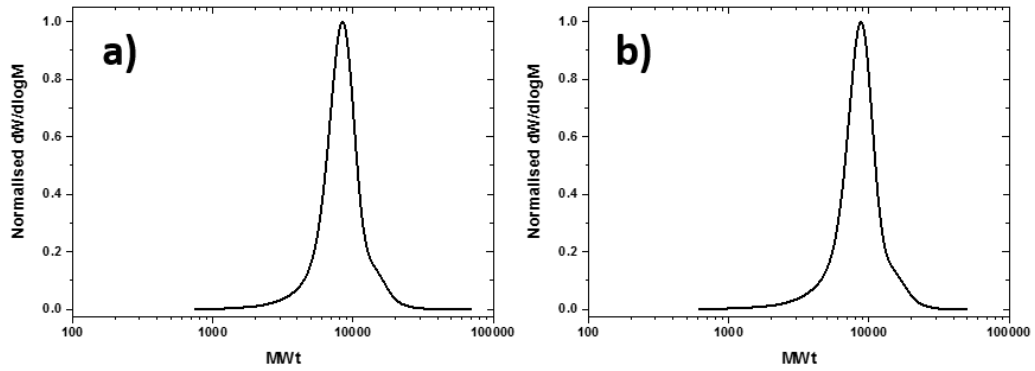


Figure 3.14: SEC analysis of well-defined polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in toluene: IPA mixtures with a) 1:1 and b) 4:1 under the following reaction conditions [MBPA]:[S]:[CuBr2]:[PMDETA]=[1]:[50]:[0.05]:[0.36].

3.2.5. Combining Optimal Conditions

Our findings that toluene and dioxane are much better solvents in mediating the controlled polymerisation of styrene while maintaining high initiator efficiency were further confirmed by replacing MBPA with EBP or BPN, as these were previously illustrated (as illustrated in section 3.2.3) to be most effective in yielding high conversions, narrow dispersities and high initiator efficiency. Both of these initiators exhibited improved initiator efficiency in dioxane and toluene (when compared to MBPA) with EBP achieving dispersities as low as 1.13 and I_{eff} = 82%. (Table 3.10, Entries 1-2 and Figure 3.15)

Table 3.10: ^{1}H NMR and SEC analysis of the polymerisation of styrene, with optimal initiator solvent combinations illustrated.[a]

Entry	Initiator	Solvent	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	I_{eff} (%)	Đ
1	EBP	Dioxane	28	23600	29200	81	1.14
2	EBP	Toluene	28	23600	28800	82	1.13
3	BPN	Dioxane	26	21900	23800	92	1.20
4	BPN	Toluene	31	26000	25800	100	1.25

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 800 and conversion was calculated *via* ^{1}H NMR.

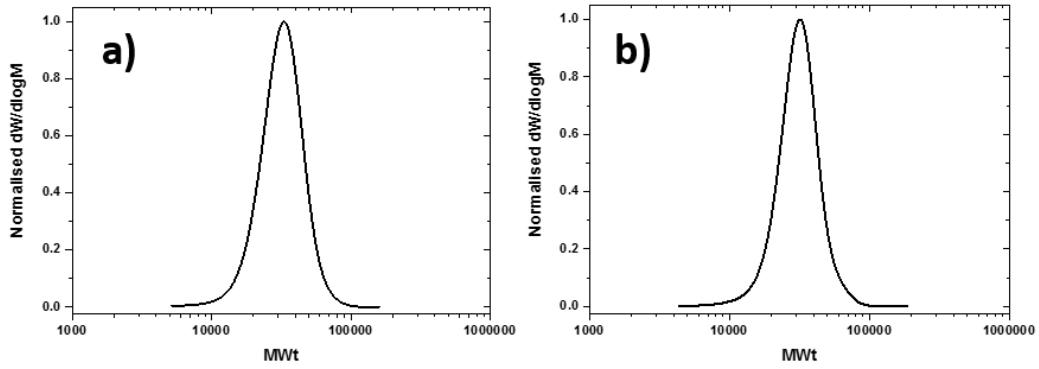


Figure 3.15: SEC analysis of polystyrene (Target DP800) prepared at 60 °C via Cu(0)-RDRP in a) dioxane and b) toluene with EBP as the initiator, under the following reaction conditions [EBP]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.36].

On the contrary, BPN yielded polystyrene with initiator efficiencies > 92% although the dispersities were ~ 1.2. (Table 3.10, Entries 3-4 and Figure 3.16)

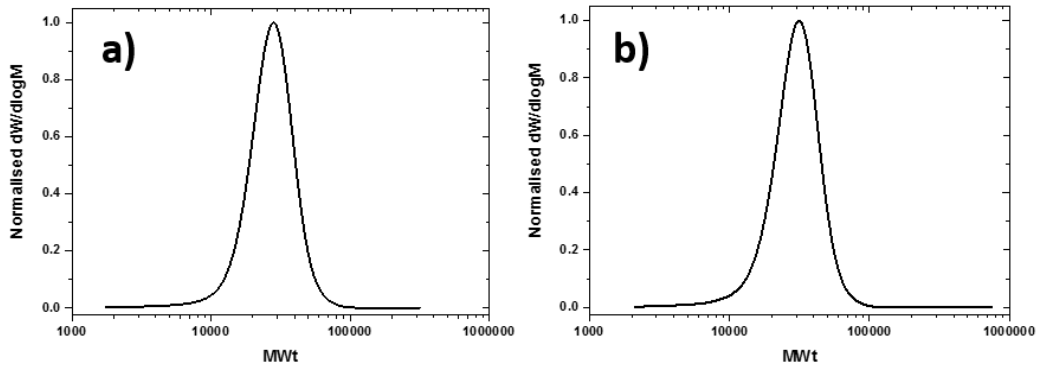


Figure 3.16: SEC analysis of polystyrene (Target DP800) prepared at 60 °C via Cu(0)-RDRP in a) dioxane and b) toluene with BPN as the initiator, under the following reaction conditions [BPN]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[800]:[0.05]:[0.36].

Thus, any combination of EBP and BPN in combination with either dioxane or toluene can be successfully employed.

3.2.6. Exploring Polymerisation in Bulk

Conventional ATRP in the absence of solvent (bulk) has been well explored, however Cu(0)-RDRP in bulk has rarely been investigated.[47] Since it was demonstrated that the nature of the solvent can have such a dramatic effect on the initiator efficiency, we decided to further simplify our system and eliminate any solvent effects. A targeted

degree of polymerisation of 800 was again chosen for this study. To our surprise, 0.36 equivalents of PMDETA with respect to initiator yielded well controlled polystyrene ($M_{n\,(SEC)}$ = 31900) with perfect initiator efficiency (~ 100%, Table 3.11, Entry 1 and Figure 3.17a). This is in contrast to when IPA or toluene were used, where 54% and 68% initiator efficiencies were observed respectively.

Table 3.11: ^{1}H NMR and SEC analysis of the polymerisation of styrene in bulk.[a]

Entry	Ligand	Initiator	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	I_{eff} (%)	Đ
1	PMDETA (36%)	MBPA	38	31900	31900	100	1.13
2		EBP	39	32700	32700	100	1.14
3		EBiB	59	46900	45100	96	1.13
4	Me_6Tren (18%)	MBPA	30	25200	28800	88	1.10
5		EBP	31	26000	26100	100	1.10
6		EBiB	60	49900	48200	97	1.16

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ and 36% PMDETA with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 800 and conversion was calculated *via* ^{1}H NMR.

EBP also gave rise to excellent initiator efficiencies (~ 100%) and narrow molecular weight distributions (Đ = 1.14) (Table 3.11, Entry 2 and Figure 3.17b). Interestingly, although EBiB was unable to successfully polymerise styrene in solution, under bulk conditions it allowed for the controlled polymerisation of styrene (Đ = 1.13) but also very good initiator efficiency was achieved (~97%) with a final $M_{n\,(SEC)}$ of 45100 (Table 3.11, Entry 3 and Figure 3.17c). This is possibly attributed to changes in the relative solubilities of Cu(I) and Cu(II) complexes in bulk (compared to solvated), which are potentially less relevant in low ppm copper systems compared to high ppm copper systems. Bulk systems have also been previously illustrated to reduce termination events, but as previously mentioned (section 1.2.2) consideration of auto-acceleration should be considered when reactions are performed in bulk.[48]

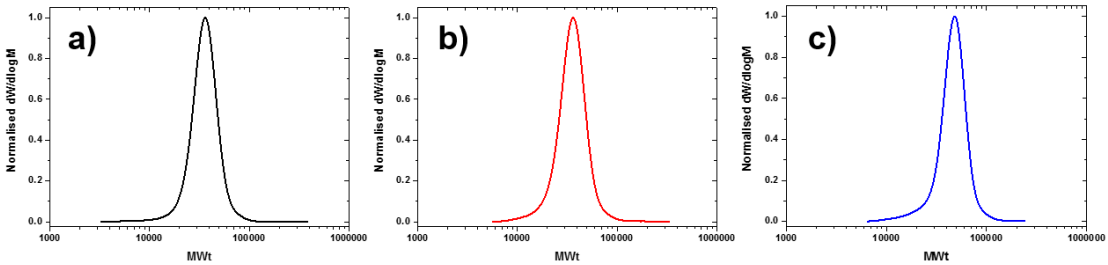


Figure 3.17: SEC chromatograms of well-defined polystyrene (Target DP800) synthesised in bulk utilising PMDETA (36%) as the ligand and a) MBPA, b) EBP and c) EBiB as the initiator.

Given the great success achieved with these bulk experiments, we hypothesised that the absence of solvent might also increase the tolerance of the system to other components. To validate our hypothesis, Me_6Tren was employed as an alternative ligand. The bulk reactions of MBPA, EBP and EBiB all resulted in controlled polymerisations with low dispersity values (< 1.16) and exceptional initiator efficiencies (~88-99%) (Table 3.11, Entries 4-6 and Figure 3.18). The greater versatility of this system compared to high copper systems and also polar solvated conditions can be attributed to the relative solubility of Cu(I) and Cu(II) complexes, with low copper concentration systems having much better relative solubilities.

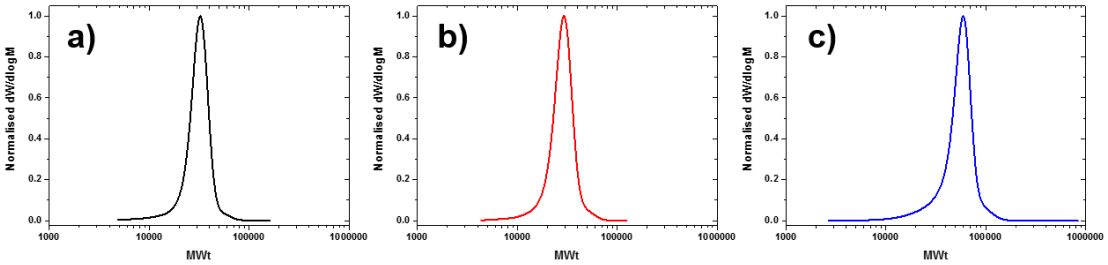


Figure 3.18*:* SEC chromatograms of well-defined polystyrene (Target DP800) synthesised in bulk utilising Me_6Tren (18%) as the ligand and a) MBPA, b) EBP and c) EBiB as the initiator.

These results demonstrate the superiority of bulk conditions for the controlled polymerisation of styrene while maintaining a balance between low dispersities and excellent initiator efficiencies for a range of initiators and ligands. Even though these results are a significant improvement on previous reports of styrene polymerisation in

ppm copper systems, it should however be noted that conversions are limited compared to anionic polymerisation, where significantly higher molecular weights can be achieved.

3.3. Conclusions

In conclusion, we have demonstrated a number of conditions that allow access to the controlled polymerisation of styrene *via* Cu(0)-RDRP. By carefully adjusting the type and concentration of ligand, the initiator choice and the solvent well-defined polystyrene can be obtained with low dispersity values and high initiator efficiency. Using increased ligand concentrations (0.72 equiv.), specific solvents (toluene, dioxane) and secondary initiators (EBP, BPN) polystyrene can be made in a facile manner. Interestingly, our best results were obtained when performing the experiments in bulk where a number of initiators and ligand were shown to facilitate the controlled polymerisation of styrene without compromising the molecular weight distributions.

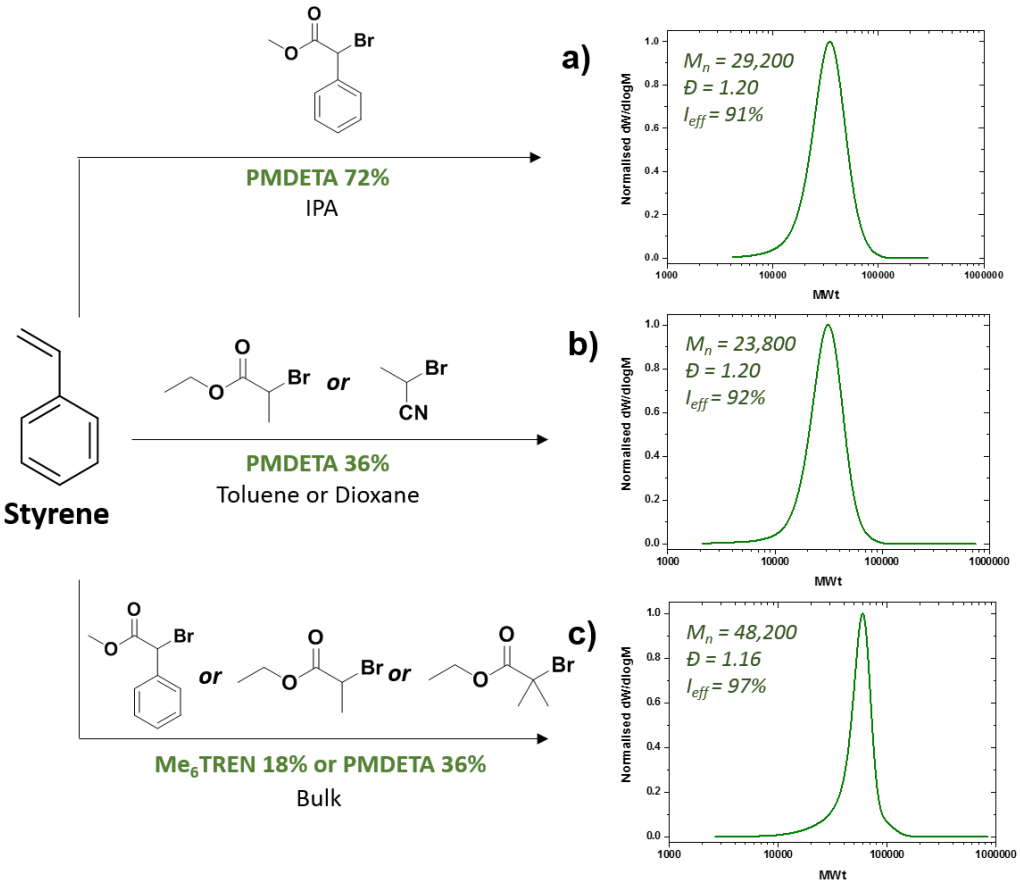


Figure 3.19: SEC chromatograms of well-defined polystyrene homopolymers synthesised via the optimised Cu(0)-RDRP conditions, namely a) increasing ligand concentration, b) optimising initiator and solvent and c) the development of a bulk polymerisation system. In all cases polymerisations were carried out at 60 °C, with 5 cm of copper wire and 5% $CuBr_2$ deactivator with respect to the initiator utilised.

3.4. Experimental Part

3.4.1. Materials

All materials were purchased from Sigma Aldrich (Merck) or VWR and used as received unless otherwise stated. All monomers were used as received, without subsequent purification. Solvents and initiators were used as purchased. *Tris*-(2-(dimethylamino)ethyl)amine (Me_6Tren) was synthesised according to previously reported literature[41] and distilled prior to use. *Tris*-(2-aminoethyl)amine (Tren) and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) were distilled prior to use. Cu(0) (gauge 0.25 mm) wire was purchased from Comax Engineered wires and purified by immersion in concentrated hydrochloric acid for 15 minutes and subsequently rinsed with water and dried prior to use.

3.4.2. Instrumentation

^{1}H NMR spectra were recorded on Bruker DPX-300 MHz or DPX-400 MHz spectrometers in $CDCl_3$. Chemical shifts are given in ppm downfield from the internal standard tetramethylsilane. Monomer conversions were determined *via* ^{1}H NMR spectroscopy by comparing the integrals of monomeric vinyl protons to polymer signals. Figure S1 illustrates a ^{1}H NMR of polystyrene synthesised. $M_{n\ (theory)}$ was calculated by multiplying the percentage conversion by the target molecular weight. Size exclusion chromatography measurements were conducted using an Agilent 390-LC MDS instrument fitted with DRI, VS, dual angle LS and dual wavelength UV detectors. The system was equipped with two PLgel 5 mm mixed-C columns (300 x 7.5 mm), one PLgel 5 µm guard column and autosampler. Narrow linear poly(styrene) standards (Agilent EasyVials) with PS molecular weights ranging from calibration between 550 g mol^{-1} and 1,568,000 g mol^{-1} were used as calibrants and fitted with a 3rd order polynomial. Samples

were run at a flow rate of 1.0 mL min^{-1} at 30 ˚C. All samples were passed through a 0.22 μm GVHP membrane prior to analysis. The mobile phase was THF with 2% TEA and 0.01% BHT as additives. Experimental molar mass ($M_{n\,(SEC)}$) and dispersity ($Đ$) values were analysed using Agilent GPC/SEC software (version 1.2). Initiator efficiency was calculated based on the ratio of the theoretical molecular weight and the molecular weight measured by SEC, using PS calibrants in all cases.

3.4.3. General Procedures

3.4.3.1. General Procedure for a Typical Cu(0)-RDRP of Styrene in Solution.

Styrene (4 mL or 3.64 g, 800 equiv.), pre-activated copper wire (5 cm), EBP (5.6 µL or 7.8 mg, 1 equiv.) or BPN (3.8 µL or 5.8 mg, 1 equiv.), $CuBr_2$ *via* a stock solution (0.49 mg, 0.05 equiv.) and either toluene or dioxane (4 mL) were added to a septum sealed vial. The copper wire was wrapped around the stirrer bar and the mixture was subsequently deoxygenated by bubbling with nitrogen for 20 min. PMDETA (3.2 µL, 0.36 equiv.) was then introduced in the vial *via* a gas-tight syringe and the polymerisation was allowed to commence at 60 ˚C for 36 h. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

3.4.3.2. General Procedure for a Typical Cu(0)-RDRP of Styrene in Bulk

Styrene (8 mL or 7.28 g, 800 equiv.), $CuBr_2$ (0.98 mg, 0.05 equiv.) and Me_6Tren (4.2 µL, 0.18 equiv.) were sonicated for 20 minutes in a glass vial so to achieve saturated solutions of Cu(II)Br_2. A stirrer bar wrapped with 5 cm of pre-activated copper wire was subsequently added to the reaction mixture and the vial sealed with a septum and subsequently deoxygenated by bubbling with nitrogen for 20 minutes. EBiB (12.8 µL or 17.0 mg, 1 equiv.) was then introduced in the vial *via* a gas-tight syringe and the

polymerisation was allowed to commence at 60 ˚C for 36 h. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

3.5. Additional Characterisation

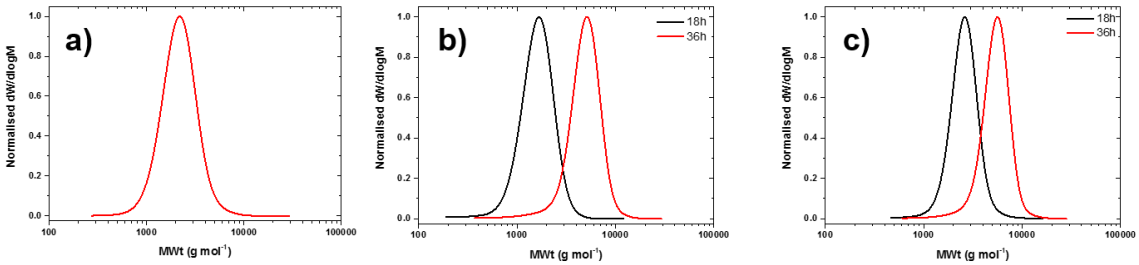


Figure 3.20: SEC analysis of polystyrene (Target DP50) prepared at a) 25 °C, b) 40 °C and c) 50 °C via Cu(0)-RDRP in IPA utilising MBPA at the initiator, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.36]. Black traces are those samples taken after 18 hours and red traces are samples taken after 36 hours.

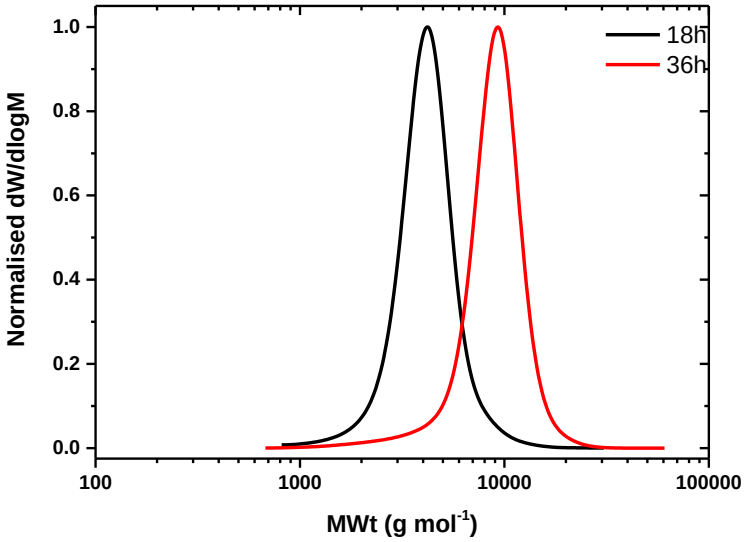


Figure 3.21: SEC analysis of polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in IPA utilising MBPA at the initiator, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.36]. The black trace is that of a sample taken after 18 hours and the red traces is that of a sample taken after 36 hours.

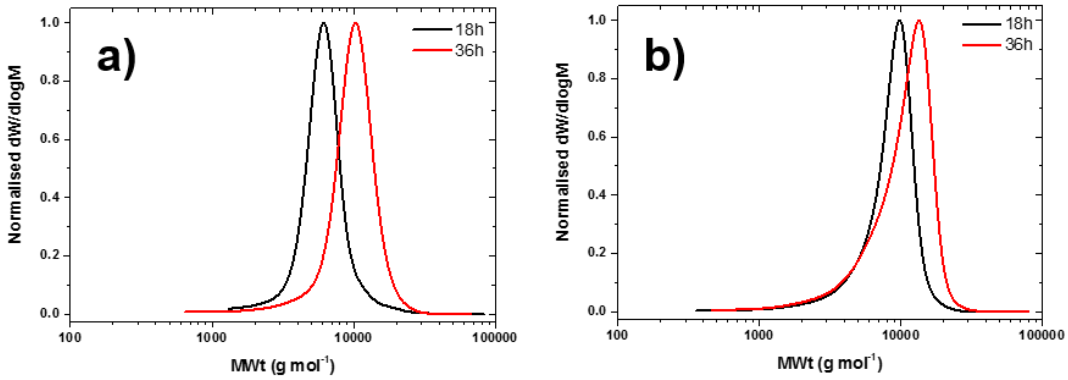


Figure 3.22: SEC analysis of polystyrene (Target DP50) prepared at a) 70 °C, b) 80 °C via Cu(0)-RDRP in IPA utilising MBPA at the initiator, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.36]. Black traces are those samples taken after 18 hours and red traces are samples taken after 36 hours.

Table 3.12: ^{1}H NMR and SEC analysis of polystyrene with target DP50 prepared via Cu(0)-RDRP in IPA, under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[L]=[1]:[50]:[0.05]:[0.36], with BPY, TPMA, cyclam and Me4cyclam respectively utilised as the ligand.[a]

Entry	Ligand	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	$Đ$
1	BPY	0	-	-	-
2	TPMA	63	3500	7100	1.58
3	Cyclam	25	1500	8000	2.38
4	Me_4Cyclam	63	3500	11100	2.39

[a]In homopolymerisations 5 cm of Cu(0) wire and 5% $CuBr_2$ with respect to initiator were utilised and samples were taken after 36 hours. The temperature was 60°C and the volume ratio of monomer to solvent was maintained at 1:1. The target DP was 50 and conversion was calculated *via* ^{1}H NMR.

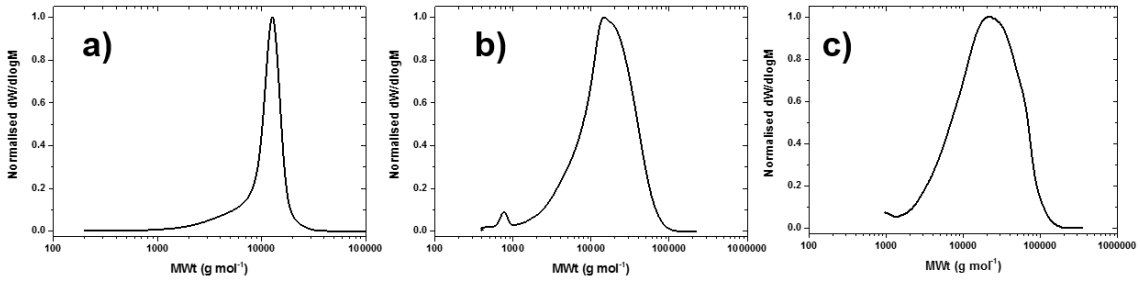


Figure 3.23: SEC analysis of polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in IPA with a) TPMA b) Cyclam and c) Me_4Cyclam utilised as the ligand.

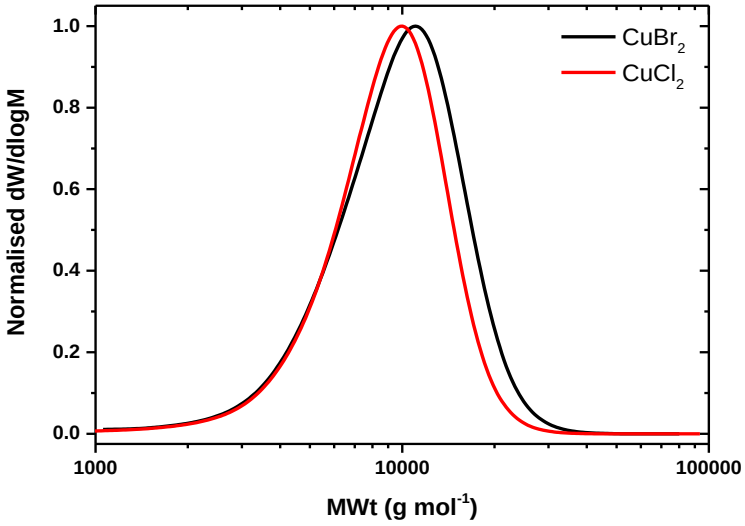


Figure 3.24: SEC analysis of polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in IPA under the following reaction conditions [Tosyl Chloride]:[S]:[CuX_2]:[PMDETA]=[1]:[50]:[0.05]:[0.36].

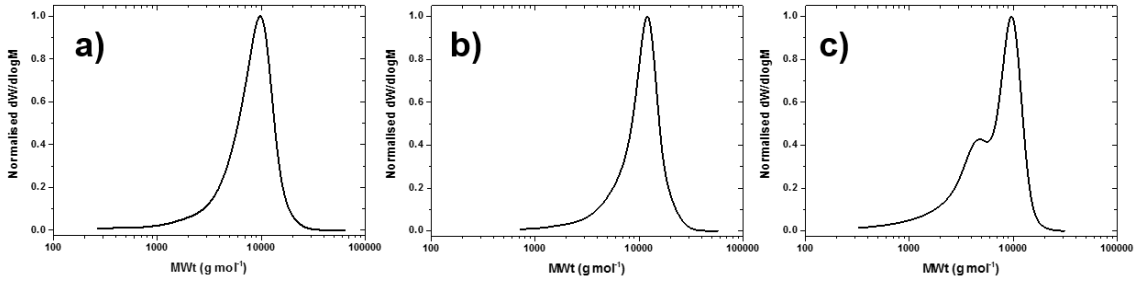


Figure 3.25: SEC analysis of uncontrolled polystyrene (Target DP50) prepared at 60 °C via Cu(0)-RDRP in a) DMSO b) DMF c) Ethanol under the following reaction conditions [MBPA]:[S]:[$CuBr_2$]:[PMDETA]=[1]:[50]:[0.05]:[0.36].

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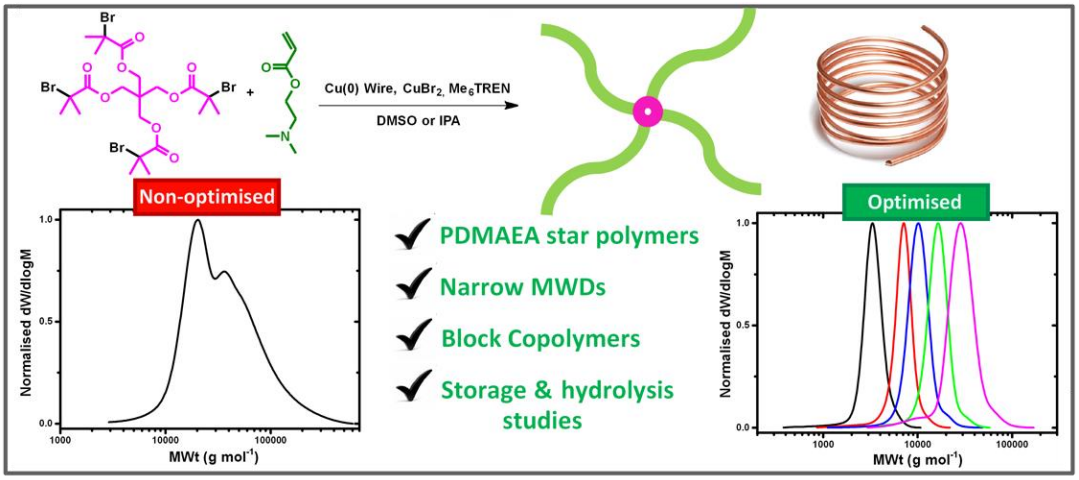
Chapter 4: Well-defined PDMAEA Stars *via* Cu(0)-Reversible Deactivation Radical Polymerisation



The Cu(0) reversible deactivation radical polymerisation of N,N'-dimethylaminoethyl acrylate in DMSO and IPA at ambient temperature using Cu(0) wire is investigated. Tetra-functional and octa-functional initiators were utilised to facilitate the synthesis of well-defined PDMAEA star homo and block copolymers with a range of molecular weights (M_n ~ 5000-41000 g mol^{-1}). Both solvents demonstrated to be excellent media for the controlled polymerisation of DMAEA yielding narrow molecular weight distributions (Đ ~ 1.1) when the reactions were ceased at ~ 40% conversion. Interestingly, at high conversions (typically > 55%) high and low molecular weight shoulders were evident by SEC when DMSO and IPA were used respectively, suggesting large extent of termination and/or side reactions at prolonged reaction times. Nevertheless, high end group fidelity could be maintained when immediate precipitation of the polymers (at lower conversion) was performed yielding low dispersed P(DMAEA-b-MA) star block copolymers (Đ < 1.19, M_n ~ 20000 g mol^{-1}). Importantly, guidelines on how to prevent hydrolysis, termination and side reactions of PDMAEA as well as how to purify and store such materials are also provided and discussed.

This Chapter is adapted from *Macromolecules*, 2016, **49** (23), 8914-8924.

4.1. Introduction

Polyamines have attracted considerable interest due to the presence of cationic nitrogen atoms that allow for pH tuning and the formation of pH responsive nanoparticles structures that self-assemble in aqueous solution.[1-3] These properties render polyamines a good candidate for a wide range of applications.[4-7] In comparison to the analogous methacrylate, PDMAEMA, PDMAEA has attracted considerable further interest due to its unique ability to hydrolyse in water. This self-catalysed mechanism yields poly(acrylic acid) and *N,N'*-dimethylaminoethanol, thus making this polymer suitable for a number of applications, where binding to a cationic polymer and subsequent release is required, for example drug or gene delivery. [8,9]

Several reversible-deactivation radical polymerisation methods have been employed in an attempt to provide PDMAEA with high end group fidelity and narrow molecular weight distributions. Cunningham and co-workers[10] utilised NMP[11] at 100°C to control the polymerisation of DMAEA, resulting in relatively low molecular weight polymers ($M_{n\,(SEC)}$ ~ 8800, $Đ$ ~ 1.29) and broad MWDs when a higher molecular weight was targeted ($M_{n\,(SEC)}$ ~ 13000, $Đ$ ~ 1.47). Importantly, the chain extension of the homopolymers/macroinitiator with butyl acrylate gave high dispersities ($Đ$ >1.4) and a significant low molecular weight shoulder, indicative of intense termination events and/or side reactions. High temperatures were used for all the experiments.[10] RAFT polymerisation[12] has also been employed for the controlled polymerisation of DMAEA. Monteiro and co-workers reported narrow MWDs ($Đ$ ~ 1.17-1.26) for low molecular weight PDMAEA ($M_{n\,(SEC)}$ ~ 3000-8600). However, no chain extensions or block copolymerisations were reported.[13] Perrier and co-workers also used RAFT to polymerise DMAEA employing a PDMS macro chain transfer agent at 70 °C. Although narrow molecular weight distributions were reported ($Đ$ ~ 1.20), again chain extensions were not

studied.[14] Additional reports[15] on RAFT, also show a preference to incorporate PDMAEA as the second or third block, instead of using it as a macroinitiator.[16,17]

The polymerisation of DMAEA by copper-mediated RDRP techniques is somewhat problematic when compared to other acrylates monomers.[18,19] This is attributed to the nucleophilic nature of the tertiary amine on the pendant groups that can react with the secondary halide on the polymer chain end. Thus, nucleophilic reactions can occur *via* intramolecular and/or intermolecular interactions.[20] Zhu and co-workers utilised ATRP[21,22] at 70 °C to synthesise PDMAEA homopolymers up to $M_{n\,(SEC)}$ ~10000 with relatively broad MWDs ($Đ$ ~ 1.43). Chain extension of PDMAEA macroinitiator was not reported.[20] Further ATRP reports utilised PDMAEA as the third block to yield well-defined materials.[23] High temperatures have been employed in all cases which could cause additional side reactions.

The use of Cu(0) in copper-mediated RDRP was reported by Matyjaszewski and co-workers in 1997[24] and was made popular in 2002[25] and 2006[26] by Percec and co-workers, who successfully illustrated the controlled polymerisation of acrylates[18,27-29] methacrylates[30,31] and acrylamides[32-34] at ambient temperatures or below with a broad range of architectures, including stars, combs, brushes and multiblock copolymers.[35-37] Monteiro and co-workers utilised Cu (0) powder to successfully polymerise DMAEA, with narrow molecular weight distributions, although only for relatively low molecular weights. ($M_{n\,(SEC)}$ ~ 9000, $Đ$ ~ 1.29).[38] However, Cu(0) wire would perhaps be a better alternative as it offers many advantages as opposed to Cu(0) powder, including facile tuning of the reaction rate, predictability, easy catalyst preparation and recyclability.[39, 40] In addition, none of the aforementioned reports, including Cu(0)-RDRP have been employed for the synthesis of PDMAEA star homo and block copolymers.

Star polymers are of particular interest both in academia and industry due to their potential applications as viscosity modifiers, catalyst supports, polymer therapeutics, drug carriers and additives.[41-45] In comparison to their linear counterparts, star polymers possess additional properties thanks to their compact structures and high arm density.[42, 46] The major challenge in the synthesis of well-defined star polymers via RDRP methodologies is bimolecular termination due to star-star coupling.[47] The high end group fidelity of Cu(0)-RDRP suggests that it could potentially be an efficient tool for the synthesis of star polymers with narrow MWDs and low coupling.[48, 49] Indeed, Cu(0)-RDRP has already been employed to yield well-defined stars,[50] including the synthesis of stars homopolymers in a biphasic system, which was shown to suppress star-star coupling. This is attributed to the reduced ability of polymeric stars in the viscous swollen monomer/polymer phase to interact with surrounding stars and the further compartmentalisation of individual stars in polymeric domains dispersed in a monomer phase may also minimise reactions between stars.[51] However, in all these reports examples non-functional monomers have been employed (typically methyl acrylate), thus limiting the applications of the resultant materials.[52]

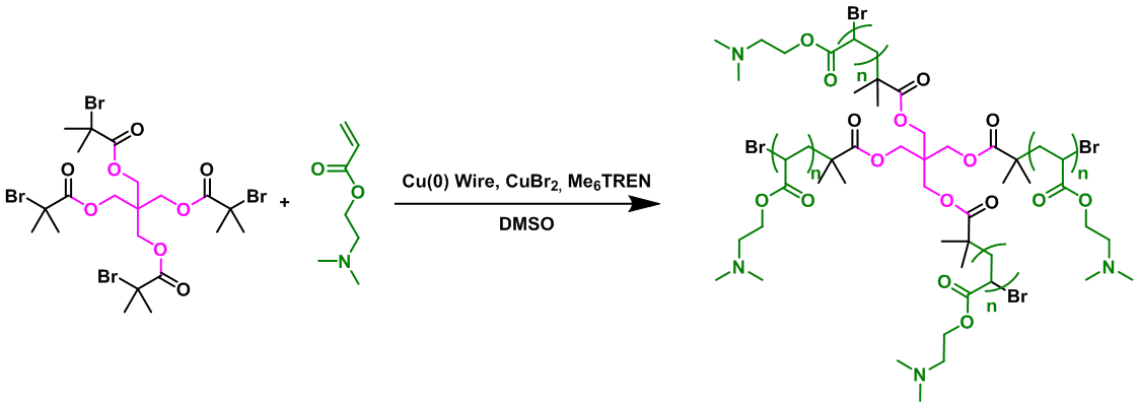
In this chapter, the Cu(0)-RDRP in dimethyl sulfoxide and isopropanol solvents is presented. All reactions are performed at ambient temperature to afford well-defined 4 and 8 arm PDMAEA stars. Polymerisation of DMAEA in either solvent using Cu(0) wire proceeds with controlled/living characteristics up to ~ 40% conversion, after which significant termination and/or side reactions start to occur as evidenced by SEC. This is highlighted in DMSO with a high molecular weight shoulder that increases throughout the polymerisation while in IPA a low molecular weight shoulder gradually forms suggesting loss of end group fidelity when longer reaction times are targeted. However, high end group fidelity can be maintained when the polymerisation is stopped at moderate

conversions (35-50%) and the purified macroinitiator can subsequently facilitate the synthesis of well-defined block copolymers. In addition, a range of molecular weights can be synthesised ($M_{n\ (SEC)}$ ~ 5000-41000), exhibiting narrow MWDs ($Đ$ ~ 1.1) in all cases. Due to the high reactivity of the tertiary amine of PDMAEA, the first instructions on how to efficiently terminate these polymerisations and subsequently purify and store the PDMAEA stars are also presented.

4.2 Results and Discussion

4.2.1. Synthesis of PDMAEA Star Homopolymers Utilising a 4-arm Initiator in DMSO

Initially, the polymerisation of DMAEA was carried out in DMSO using Cu(0) wire, a *tetra*-functional initiator (1,1,1,1-*tetra*(methyl-2-methyl-2-bromopropionate), $CuBr_2$ and Me_6Tren at ambient temperature, under the following reaction conditions: [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.40]:[0.72] (Scheme 4.1).



Scheme 4.1: PDMAEA synthesis from a 4-arm initiator via Cu(0)-RDRP.

It should be noted that 0.10 equiv. of $CuBr_2$ and 0.18 equiv. of Me_6Tren were used relative to each initiating site as these ratios have been shown to maintain high end group fidelity.[48] Kinetic experiments revealed that the polymerisation proceeded with a relatively slow rate, when compared with other acrylate analogues such as methyl acrylate[53]with 68% conversion achieved in 4 h and a final conversion of 86% even when the reaction was left to proceed overnight (Table 4.1, Figure 4.1a). Interestingly, $\ln[M]_t/[M]_0$ increases linearly with time up until ~41% conversion (~ 1.5 h, $Đ$ ~ 1.13, Figure 4.1a) which is consistent with a constant concentration of propagating radicals suggesting a controlled/living polymerisation. SEC chromatograms (up to 2 h) indicate a shif to higher molecular weights with increasing conversion while the dispersities remain low ~ 1.10 (Figure 4.1c). It should be noted that triple detection SEC analysis followed

by subsequent use of the Zimm Stockmyer equation was not carried out to calculate the number of arms, as it has previously been illustrated to result in significant error (greater than ±1 arm).[54] An alternative method for the analysis of the number of arms and the molecular weight distribution of individual arms would be to incorporate a degradable functionality within the core of the polymer, for example disulfide linkages.

Table 4.1: **:** Kinetic experiment illustrating the Cu(0)-RDRP of DMAEA in DMSO utilising the tetra-functional initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.40]:[0.72].[a]

Entry	Time (h)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	Đ
1	0.5	21	4200	3100	1.08
2	1	30	6000	4700	1.08
3	1.5	41	8200	6000	1.10
4	2	49	9800	7300	1.13
5	3	63	12600	8300	1.28
6	4	68	13600	9500	1.31
7	18	86	17200	16200	1.99

[a]5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to each initiating site was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to DMSO was maintained at 1:1. The target molecular weight was 20000 g mol^{-1} and conversion was calculated via ^{1}H NMR.

Whilst there is some deviation between the theoretical and experimental values, it is well known that star polymers adopt different hydrodynamic volumes than their linear counterparts which are typically used for SEC calibration and also the comparison of PDMAEA to PMMA standards will also result in further deviations.[55, 56] Beyond 1 hour of reaction time a gradual broadening of the molecular weight distributions was observed resulting in bimodality and a dispersity greater than 1.3 after 4 hours and a final dispersity of 2 for the overnight sample (~ 86% conversion, Table 4.1). Importantly, SEC analysis

revealed an obvious high molecular weight shoulder which is increasing throughout the reaction (Figure 4.1c). This was attributed to the reactivity of amine functionalities with bromine end-groups on neighbouring star molecules, in addition to typical star-star radical coupling reactions commonly seen during the synthesis of star polymers in radical polymerisation, .[57] No low molecular weight shoulders were detected.

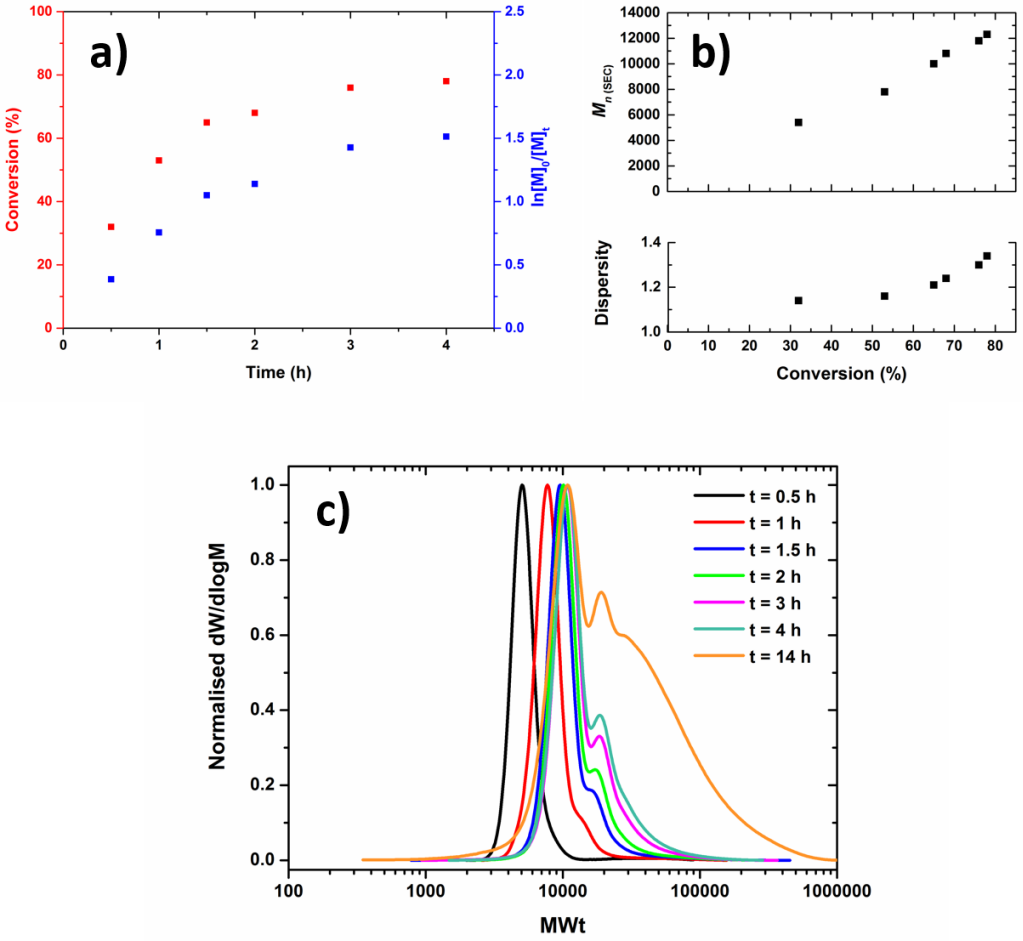


Figure 4.1: Kinetic data for the Cu(0)-RDRP of DMAEA in DMSO utilising 4-arm initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.40]:[0.72].

Interestingly, when a linear initiator was employed, broad molecular distributions were also observed at higher conversions (Tables 4.9-4.10 and Figures 4.14-4.18). This data suggest that the polymerisation of this monomer using either a linear or a star initiator exhibit significant side reactions, although in the case of the star polymers additional coupling is observed. In addition, MALDI-TOF MS was conducted where the main two

polymer distribution correspond to PDMAEA terminated with a bromine end group (with either a sodium or potassium adduct) (Figure 4.19).

Thus it is apparent that to synthesise well-defined PDMAEA stars, the reactions must be quenched at moderate conversions (up to 40%) in order to maintain low dispersities and good control over the polymerisation ($M_{n\,(SEC)}$ ~ 7300, $Đ$ ~ 1.13). In order to probe the potential of Cu(0)-RDRP in maintaining control for both lower and higher molecular weights a range of polymerisations were conducted targeting degrees of polymerisation from 35 to 560 (Target MWt ~ 5000-80000 g mol^{-1}).

Table 4.2: *^{1}H NMR and* SEC analysis of 4-arm PDMAEA with various DP prepared via Cu(0)-RDRP in DMSO under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[X]:[0.40]:[0.72].[a]

Entry	Target MWt (g mol^{-1})	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	$Đ$
1	5000	50	2500	3200	1.10
2	10000	56	5600	6600	1.09
3	20000	49	9800	9700	1.10
4	40000	43	17200	14600	1.14
5	80000	44	35200	25500	1.20

[a]In all polymerisations 5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to each initiating site was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to DMSO was maintained at 1:1. Conversion was calculated via ^{1}H NMR.

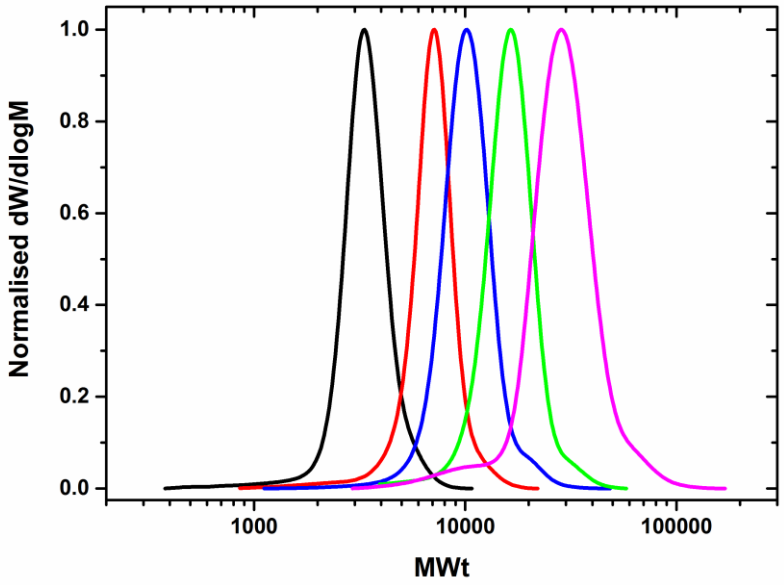


Figure 4.2: SEC analysis of PDMAEA with various DP prepared via Cu(0)-RDRP in DMSO.

The ratio of [I]:[DMAEA]:[$CuBr_2$]:[Me6Tren]=[1]:[*DP*]:[0.40]:[0.72] was kept constant for each polymerisation and the reactions were stopped typically between 40-50% of conversion in order to suppress star-star coupling reactions. In all cases, well-defined PDMAEA in various molecular weights ($M_{n\,(SEC)}$ ~ 3000-26000) with dispersities as low as 1.10 (Table 4.2 and Figure 4.2) could be attained demonstrating the advantages of Cu(0) wire over Cu(0) powder, which has previously employed by Monteiro and co-workers.[38]

4.2.2. Synthesis of PDMAEA Star Homopolymers Utilising a 4-arm Initiator in IPA

As longer reaction times lead to the loss of the constant radical concentration and coupling reaction between stars (both radical coupling reactions and the quarterisation reaction between tertiary amines and the bromine end group) the polymerisation had to be ceased at ~ 40% followed by the purification of the macroinitiator (via precipitation) in order to maintain the high end group fidelity required to facilitate the synthesis of block

copolymers. However, purification of the polymers from DMSO was found to be challenging due to the low miscibility of this solvent with all the solvents employed for the precipitation of PDMAEA, including heptane, hexane and diethyl ether. Even after multiple precipitations there was significant DMSO present in the polymer, so it was proposed an alternative solvent could be used to circumvent this purification issue. IPA was selected as this solvent has previously been successfully utilised for the controlled polymerisation of a range of vinyl monomers with Cu(0)-RDRP and has the significant advantage that it can simply be removed post polymerisation (in contrast to DMSO, DMF, TFE etc) by blowing with nitrogen or rotary evaporation (low temperatures should be used). In addition, due to the significant amount of coupling reactions observed in DMSO reactions at higher conversions, it was hypothesised that using IPA may lead to a slower polymerisation rate with a lower overall concentration of radicals. This potentially would result in increased control due to the lower polarity of IPA, the lower amount of disproportionation and therefore additional stabilisation of Cu(I)Br or a slower rate of side reactions (for example nucleophilic substitution reactions) in protic compared to aprotic solvents. We anticipated that the Cu(0)-RDRP of DMAEA in IPA could be successfully achieved either *via* retention of the polymers solubility throughout the polymerisation or the capacity of IPA to support a self-generating biphasic system as previously reported.[51] Furthermore IPA was reported as a polar solvent that has been used to reduce the dispersity of polymers synthesised by Cu(0)-RDRP and does not undergo transesterification with DMAEA.[58]

When the same conditions used for the polymerisation in DMSO were employed for the polymerisation in IPA, ([I]:[DMAEA]:[$CuBr_2$]:[Me6Tren]=[1]:[140]:[0.40]:[0.72]), the reaction proceeded with slower polymerisation rates achieving 32% conversion in 2 h (as opposed to 49%

conversion for DMSO) and 49% conversion in 4 h but a narrow molecular weight distribution was maintained with a dispersity of 1.15. This slower polymerisation rate can be further illustrated by the lower k_p^{app} value in IPA, (k_p^{app} = 5.53 x 10^{-5} s^{-1}) in comparison to DMSO (k_p^{app} = 9.20 x 10^{-5} s^{-1}). Similarly to DMSO, when the polymerisation was sampled the following day broader MWDs ($Đ$ ~ 1.60) were observed (Table 4.3).

Table 4.3: : Kinetic experiment illustrating the Cu(0)-RDRP of DMAEA in IPA utilising the tetra-functional initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.40]:[0.72].[a]

Time (h)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	$Đ$
0.5	8	1600	1700	1.08
1	16	3200	3000	1.06
1.5	25	5000	4400	1.05
2	32	6400	5300	1.05
3	45	9000	6200	1.05
4	49	9800	6600	1.15
18	64	12800	8200	1.44
36	78	15600	8900	1.59

[a]5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to each initiating site was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to IPA was maintained at 1:1. The target molecular weight was 20000 g mol^{-1} and conversion was calculated via ^{1}H NMR.

However, coupling reactions (quarterisation reactions between tertiary amine and bromine end-groups) between star molecules was significantly suppressed in the polymerisation with IPA with only a negligible high molecular weight shoulder observed on the SEC trace (Figure 4.3c). It is noted that the reaction mixture appears cloudy/heterogeneous post polymerisation, although the formation of two discrete phases was not observed. On the contrary, a low molecular weight shoulder was evident indicating a small extent of termination during the polymerisation which was further increased when the reaction was left to proceed overnight. Careful kinetic analysis of the

polymerisation in IPA revealed a similar trend with the DMSO system, where a linear increase in M_n with conversion and a largely first order dependence on both monomer and propagating radical up to ~45% conversion (Figures 4.3a-b). The discrepancy between the theoretical and the experimental molecular weight is again attributed to the difference in hydrodynamic volumes of the star polymers compared to the linear calibrants utilised in the SEC. It is also worthy of note that in this study PMMA calibrants were utilised so there would be some error in how this polymer travels through the column of the SEC in comparison to that of PDMAEA.[55, 56]

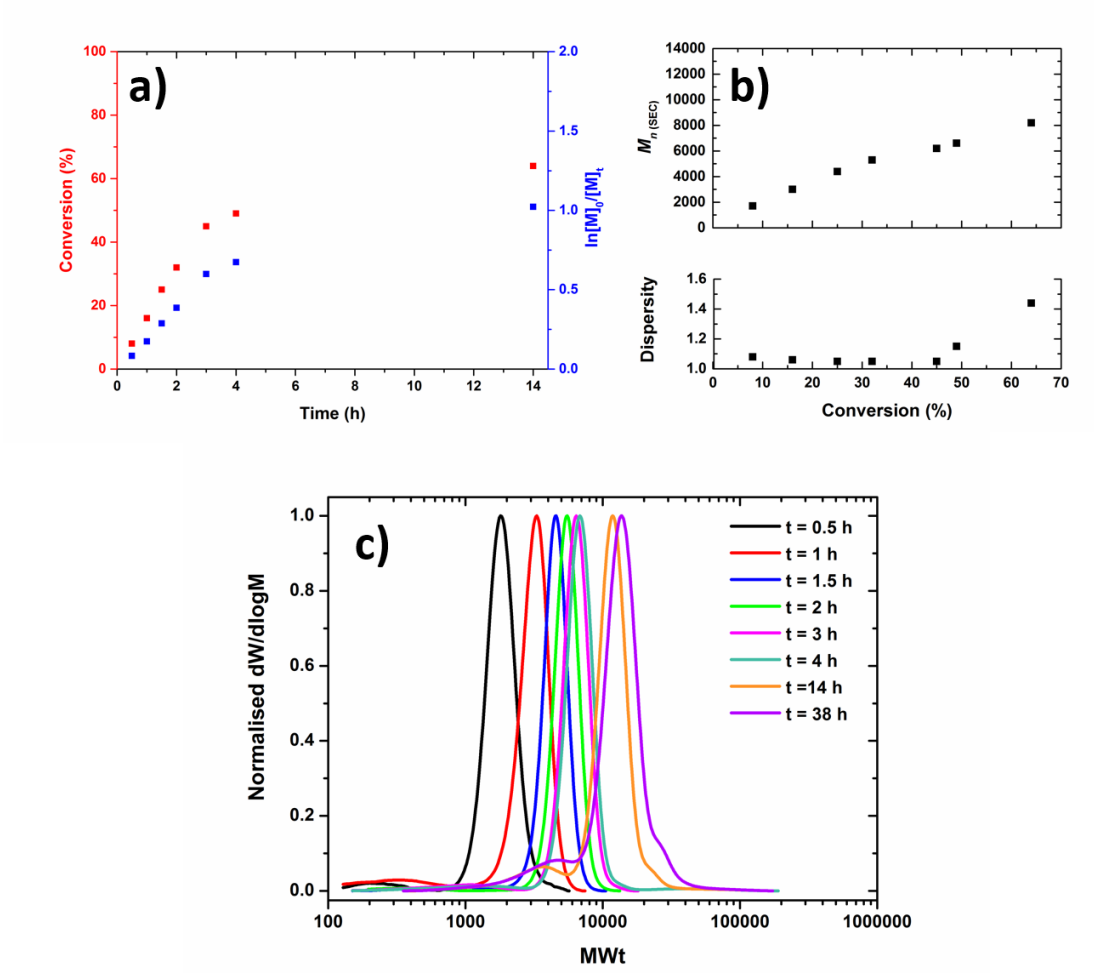


Figure 4.3: Kinetic data for the Cu(0)-RDRP of DMAEA in IPA utilising the tetra-functional initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.40]:[0.72]

A range of molecular weights were also targeted, demonstrating the capacity of IPA to support the synthesis of well-defined PDMAEA of various DPs given that the conversions were maintained at moderate levels (30-50%) (Table 4.4 and Figure 4.4).

Table 4.4: ^{1}H NMR and SEC analysis of 4-arm PDMAEA with various DP prepared via Cu(0)-RDRP in IPA under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[X]:[0.40]:[0.72].[a]

Target MWt (g mol^{-1})	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	Đ
5000	47	2400	3600	1.06
10000	53	5300	6600	1.04
20000	42	8400	9000	1.07
40000	35	14000	13300	1.15
80000	31	24800	18000	1.16

[a]In all polymerisations 5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to each initiating site was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to IPA was maintained at 1:1. Conversion was calculated via ^{1}H NMR.

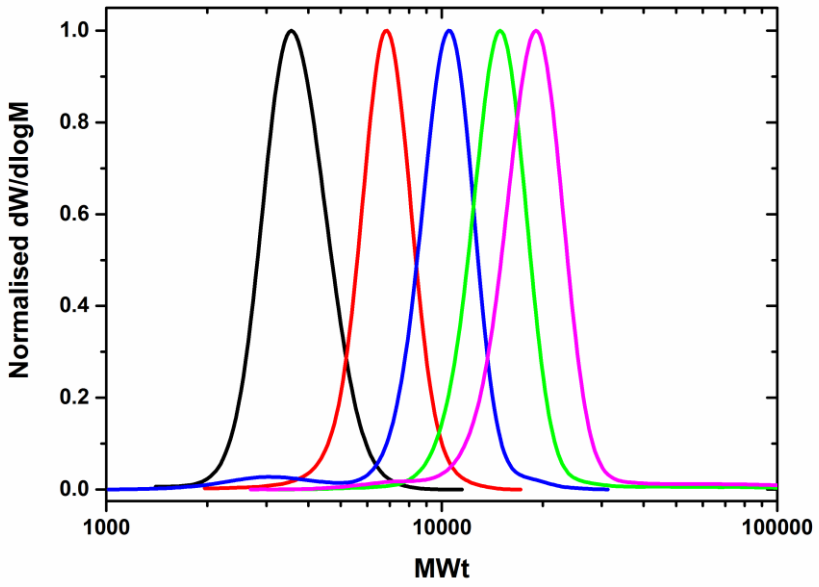
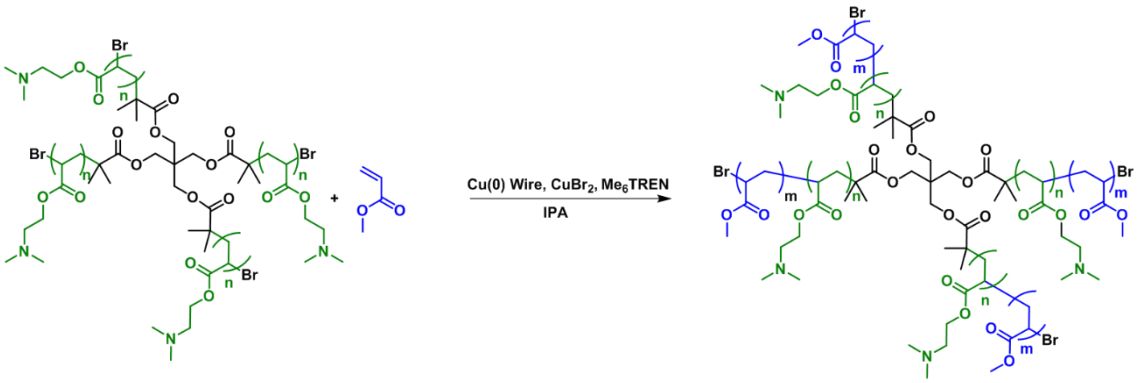


Figure 4.4: SEC analysis of PDMAEA with various DP prepared via Cu(0)-RDRP in IPA.

4.2.3. Synthesis of P(DMAEA-*b*-MA) Star Copolymers Utilising a 4-arm Initiator

Switching from DMSO to IPA allowed for the straight forward isolation of the PDMAEA by precipitation (see subsequent section for further details) at ~ 40% of

conversion ($M_{n\ (SEC)}$ ~ 9100, $Đ$ ~ 1.07) which was subsequently employed as the macroinitiator for the block polymerisation with methyl acrylate (Scheme 4.2).



Scheme 4.2: P(DMAEA-*b*-MA) synthesis from a 4-arm PDMAEA macroinitiator via Cu(0)- RDRP.

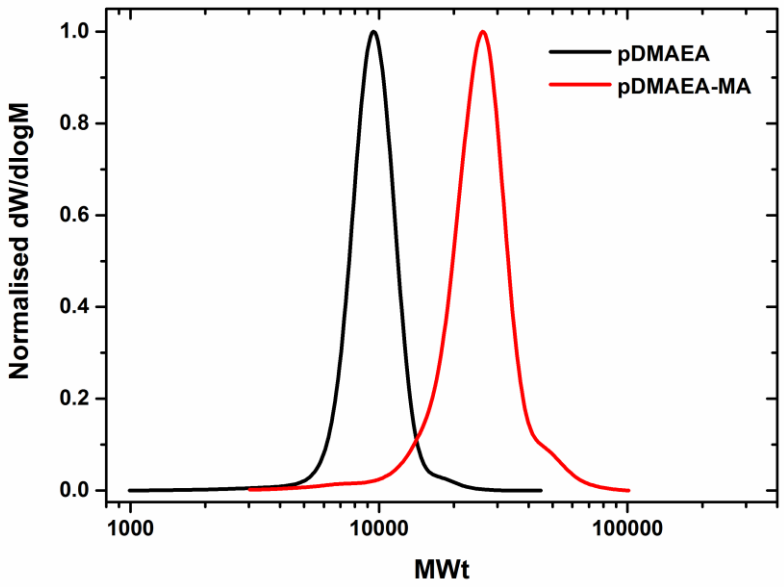


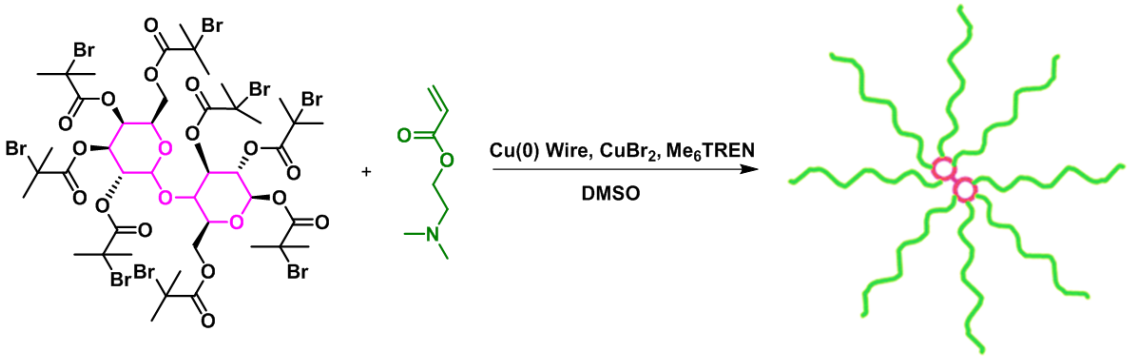
Figure 4.5: SEC of the block copolymerisation of methyl acrylate from a 4-arm PDMAEA macroinitiator in IPA via Cu(0)-RDRP.

The PDMAEA homopolymer was successfully chain extended (chain extension was also performed in IPA) with SEC revealing a nearly complete shift of the molecular weight after 3 h whilst maintaining low dispersity ($Đ$ ~ 1.15) and a final $M_{n\ (SEC)}$ of ~ 23500 (Figure 4.5). Thus, well-defined P(DMAEA-*b*-MA), Figures 4.5 and 4.21) star copolymers could be obtained for the first time and in a facile manner. Interestingly, the reduced star-star coupling observed in both the homo and block copolymerisation further

confirms the advantage of heterogeneous systems for the controlled polymerisation of star copolymers in comparison with homogeneous media.[51]

4.2.4. Synthesis of PDMAEA Star Homo and Block Copolymers Utilising an 8-arm Initiator

In order to obtain stars with an increased number of arms, an 8-arm lactose initiator (*octa*-O-isobutyryl bromide lactose initiator) was utilised by adjusting the previously employed reaction conditions for 8 initiating sites ([I]:[DMAEA]:[$CuBr_2$]:[Me6Tren]=[1]:[140]:[0.80]:[1.44], Scheme 4.3).



Scheme 4.3: PDMAEA synthesis from an 8-arm initiator via Cu(0)- RDRP.

The polymerisations were carried out in both DMSO and IPA, where a higher rate of polymerisation was evident for both solvents in comparison with the 4-arm star analogues. It is noted that increased k_p^{app} values are obtained for the 8-arm star polymers, which is due to the higher concentration of radicals generated in these systems. For example in DMSO k_p^{app} for the 8-arm star polymer is 1.32 x 10^{-4} s^{-1}, in comparison to 9.20 x 10^{-5} s^{-1} for the 4-arm star and 3.04 x 10^{-5} s^{-1} for the linear polymer. This was attributed to the greater concentration of bromines which results in higher concentration of radicals during polymerisation. Specifically, in DMSO 53% conversion was attained within 1 h ($Đ$ ~ 1.16) as opposed to 30% conversion when the 4-arm initiator was employed.

Similarly, when DMSO was utilised as the solvent slightly higher polymerisation rates were attained. Kinetic experiments were also performed, mirroring the results obtained for the 4-arm star initiator (Tables 4.5-4.6 and Figures 4.6-4.7). When the synthesis of the 8-arm stars was performed in DMSO, a high molecular weight shoulder could be observed in the SEC which increased throughout the reaction yielding polymers with very broad molecular weight distributions when left to react for prolonged periods of time (Overnight conversion 90%, $Đ$ ~ 2.75, Figure 4.6c). However, when the reaction was stopped at 53% conversion, well-defined PDMAEA stars could be obtained with $M_{n\,(SEC)}$ ~ 7800 and a final dispersity of 1.16.

Table 4.5: Kinetic experiment illustrating the Cu(0)-RDRP of DMAEA in DMSO utilising the octa-functional initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.80]:[1.44].[a]

Time (h)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	$Đ$
0.5	32	6400	5400	1.14
1	53	10600	7800	1.16
1.5	65	13000	10000	1.21
2	68	13600	10800	1.24
3	76	15200	11800	1.30
4	78	15400	12300	1.34
18	90	18000	15700	2.75

[a]5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to each initiating site was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to DMSO was maintained at 1:1. The target molecular weight was 20000 g mol^{-1} and conversion was calculated via ^{1}H NMR.

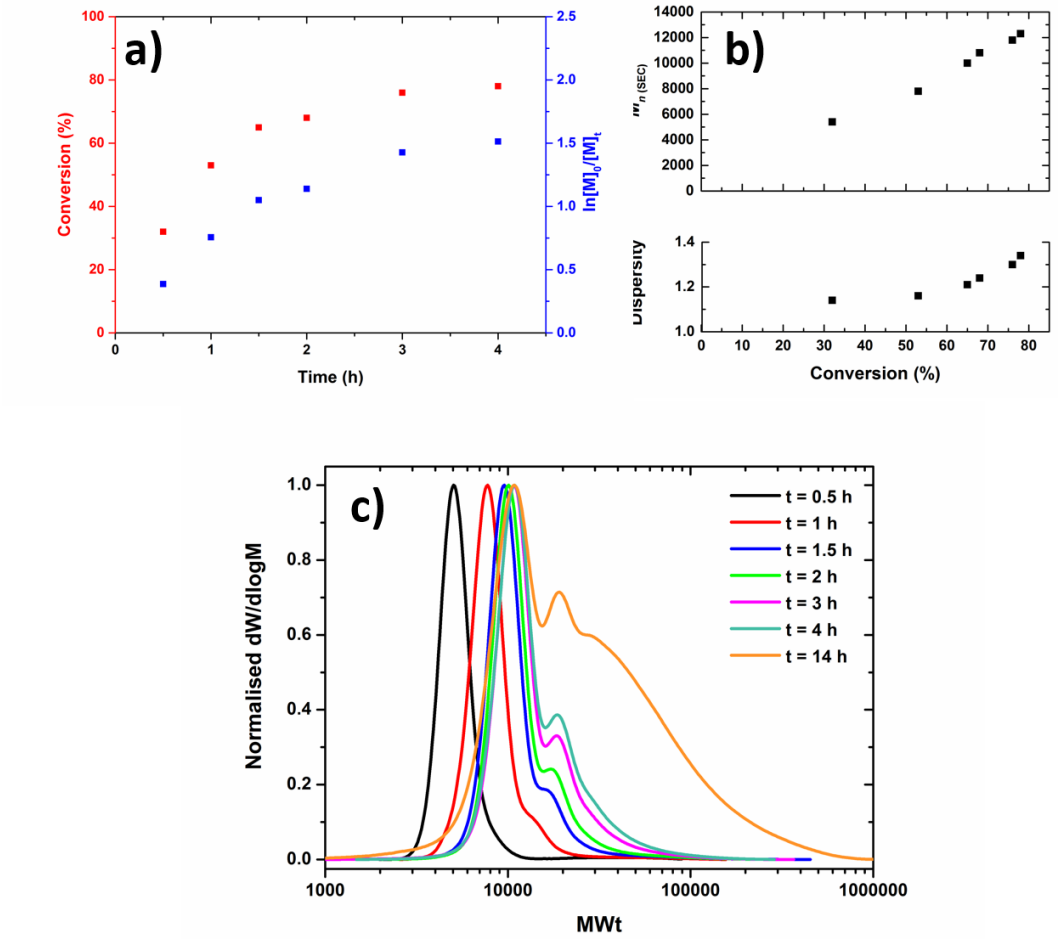


Figure 4.6: Kinetic data for the Cu(0)-RDRP of DMAEA in DMSO utilising the octa-functional initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.80]:[1.44].

In contrast to DMSO, IPA facilitates the synthesis of PDMAEA stars with less pronounced high molecular weight shoulders and lower final dispersities ($Đ$ ~ 1.48 after 16 h of reaction, Figures 4.7a-c), further highlighting the capability of IPA to reduce coupling reactions between star polymers when phase separation occurs during the polymerisation. It should however be noted that a small, yet reproducible, low molecular weight shoulder could be observed in this solvent suggesting premature termination events. Nevertheless, when the reaction was stopped at ~ 53% conversion, PDMAEA stars with low dispersities could be obtained ($Đ$ ~ 1.08, $M_{n\,(SEC)}$ ~ 6800).

Table 4.6: Kinetic experiment illustrating the Cu(0)-RDRP of DMAEA in IPA utilising the octa-functional initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.80]:[1.44].[a]

Time (h)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	Đ
0.5	11	2200	2600	1.05
1	19	3800	3800	1.04
1.5	23	4600	4900	1.04
2	27	5400	5600	1.04
3	40	8000	6500	1.05
4	53	10600	6800	1.08
18	79	15800	8900	1.48
36	94	18800	9100	1.85

[a]5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to each initiating site was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to IPA was maintained at 1:1. The target molecular weight was 20000 g mol^{-1} and conversion was calculated via ^{1}H NMR.

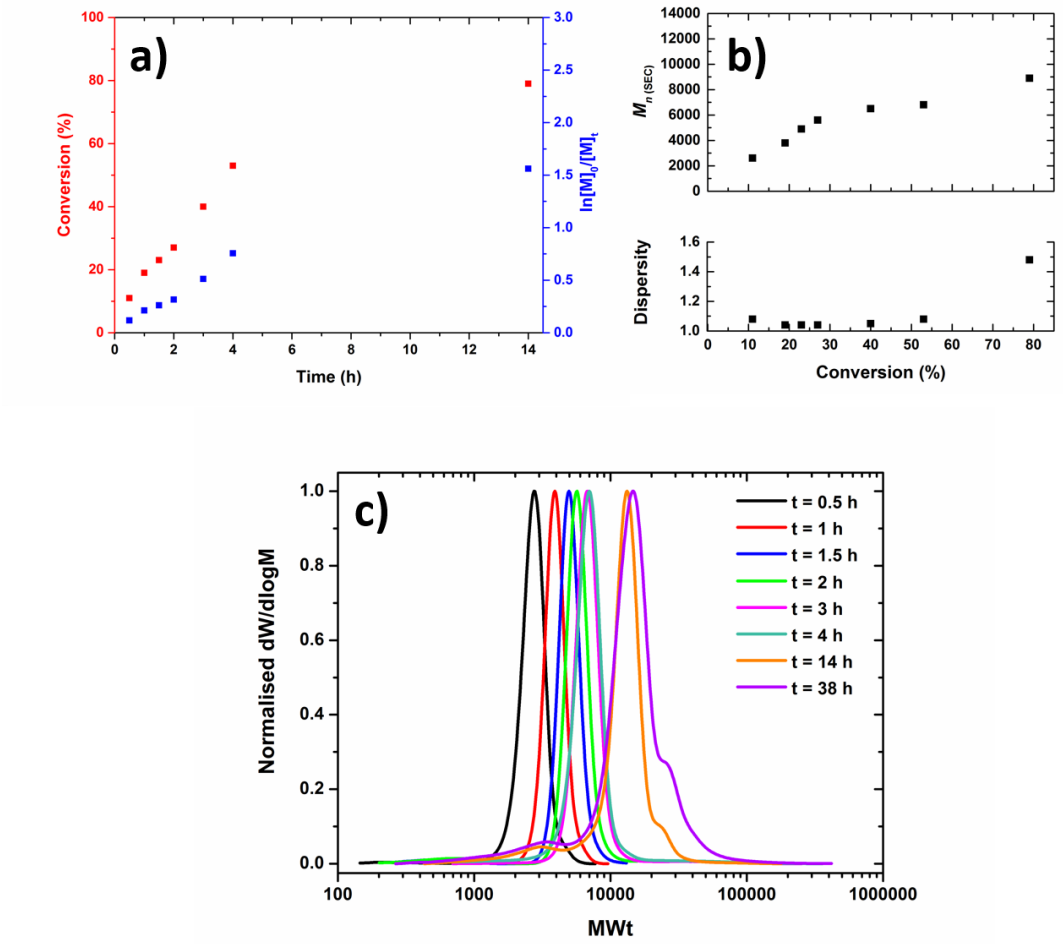


Figure 4.7: Kinetic data for the Cu(0)-RDRP of DMAEA in IPA utilising the octa-functional initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.80]:[1.44].

Higher molecular weight polymers were subsequently obtained by targeting higher degrees of polymerisation, yielding well-defined polymers up to $M_{n\,(SEC)}$ ~ 41000 and $Đ$ ~ 1.08 (Table 4.7 and Figure 4.8). It should be noted that the discrepancy between theoretical and actual molecular weight by SEC is more significant for 8-arm stars than 4-arm stars due to greater differences in hydrodynamic radius.

Table 4.7: ^{1}H NMR and SEC analysis of 8-arm PDMAEA with various DP prepared via Cu(0)-RDRP in DMSO and IPA under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[X]:[0.80]:[1.44].[a]

Entry	Solvent	Target MWt (g mol^{-1})	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	Đ
1	DMSO	10000	40	4000	5500	1.10
2	DMSO	20000	38	7600	7300	1.06
3	DMSO	40000	28	11200	9300	1.10
4	DMSO	100000	28	28 000	19200	1.10
5	DMSO	200000	34	68000	41000	1.10
6	IPA	10000	25	2500	4800	1.04
7	IPA	20000	26	5200	6600	1.05
8	IPA	40000	32	12800	10300	1.09
9	IPA	100000	26	26000	18100	1.06
10	IPA	200000	24	48000	30200	1.07

[a]In all polymerisations 5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to each initiating site was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to DMSO or IPA was maintained at 1:1. Conversion was calculated via ^{1}H NMR.

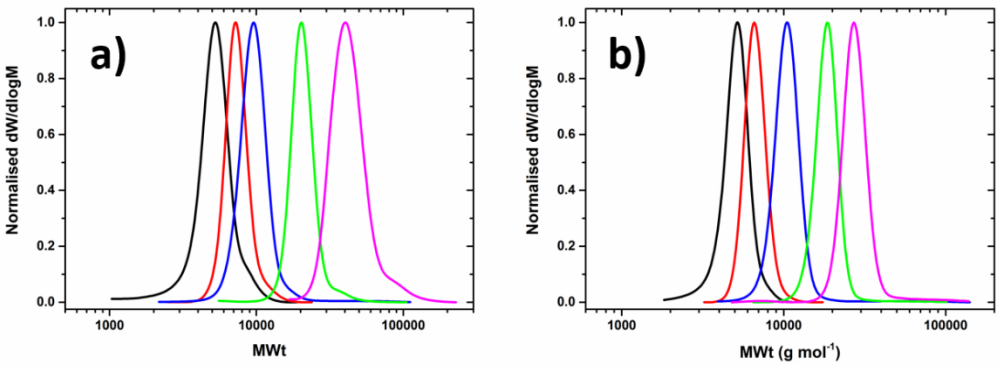


Figure 4.8: SEC analysis of PDMAEA with various DPs prepared via Cu(0)-RDRP in a) DMSO and b) IPA utilising an 8-arm initiator.

Chain extension of PDMAEA ($Đ$ ~ 1.16, $M_{n\,(SEC)}$ ~ 11100, Figure 4.20) with MA yielded well-defined P(DMAEA-*b*-MA) with $Đ$ ~ 1.19 and $M_{n\,(SEC)}$ ~ 19000 (Figures 4.8 and 4.23), demonstrating high end group fidelity of PDMAEA 8-arm macroinitiator.

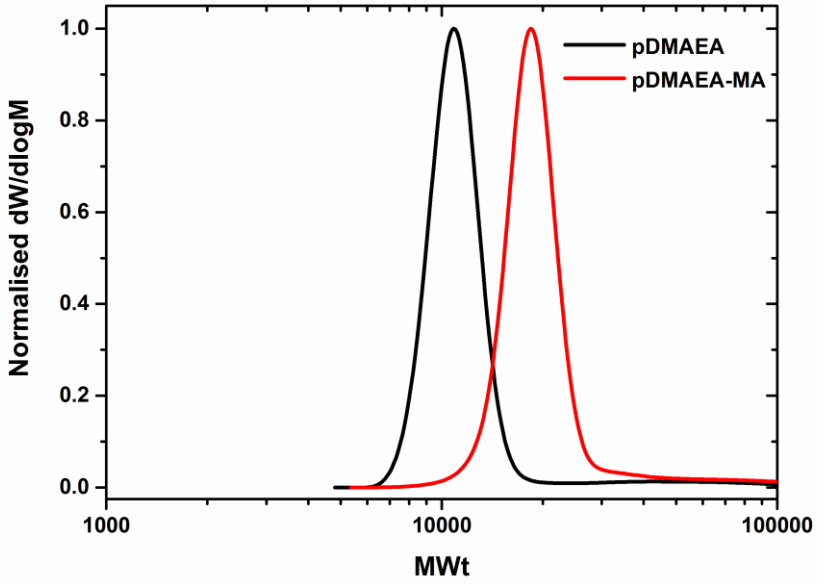


Figure 4.9: SEC of the block copolymerisation of methyl acrylate from an 8-arm PDMAEA macroinitiator in IPA via Cu(0)-RDRP.

4.2.5. Guidelines for Termination and Purification of PDMAEA Stars

As these polymers present broader MWDs with increasing reaction time (especially in the case of DMSO), it is essential to terminate the reaction at an early stage. In order to identify the best way to prevent subsequent polymerisation, 4 different samples were collected after ~ 1.5 h of polymerisation of DMAEA in DMSO (Figure 4.10a). The first sample was analysed instantly by NMR and SEC revealing ~ 42% of conversion and $Đ$ ~ 1.05 respectively. The second sample was stored in a vial at ambient temperature for ~ 18 h prior to NMR and SEC analysis. Despite the exposure in oxygen and the absence of copper wire from the system, ~ 77% of conversion was confirmed by NMR while SEC presented a highly dispersed polymer with significant high molecular weight shoulder ($Đ$ ~ 2.57). This could be attributed to the slow generation of radicals *via* light and the

subsequent free radical polymerisation of remaining DMAEA monomer or the uncontrolled propagation of existing polymer chains.[59, 60] However, when the sample was kept in the dark the same phenomenon was observed suggesting continuation of the polymerisation even in the presence of oxygen (Conversion 70%, $Đ$ = 2.97). We managed to circumvent this by diluting the third and fourth sample with $CHCl_3$ and IPA respectively, where analysis of the two samples the following day showed that both the low dispersity ($Đ$ ~ 1.05) and the conversion were maintained in both cases. This suggests that a side reaction is occurring, probably either an intermolecular or intramolecular substitution, which is slowed down by dilution. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis was also conducted revealing < 1 % of the initial copper content (5.9 ppm) and thus suggesting that copper might be associated to the side reaction, although the mechanism is unknown and out of the scope of this chapter. Alternatively, TEMPO can be used to end cap the polymer chain end which also resulted in maintaining narrow MWDs (Figure 4.10a).[61] It is noted that for the case of IPA, no significant high molecular weight shoulder is observed and there is no further increase in the conversion despite the 4 different ways to store this material (Figure 4.10b).

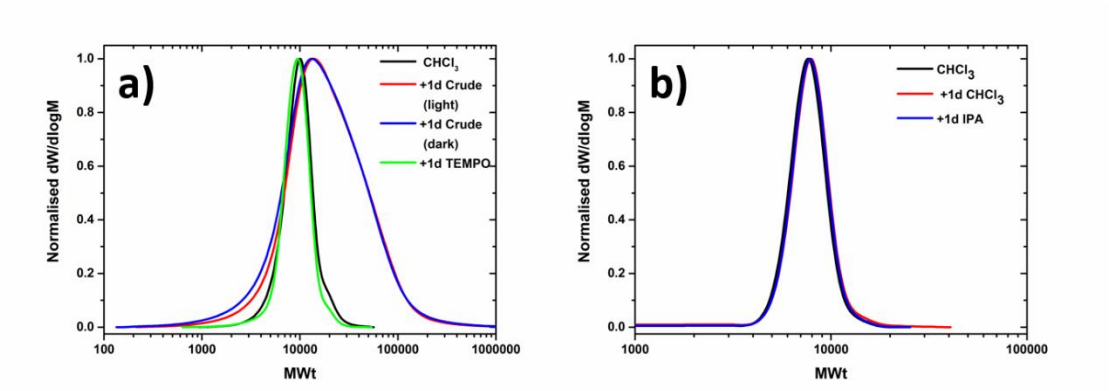


Figure 4.10: SEC traces illustrating a) the effect of storing the polymer in crude form and end-capping with TEMPO b) the effect of diluting the crude polymer with either $CHCl_3$ or IPA.

As termination and purification of these materials can be rather challenging, we would like to provide some guidelines on how to remove the remaining monomer, as well

as how to precipitate low molecular weight tailing when the polymerisation of DMAEA is performed in IPA. Once the desired conversion is reached (*e.g.* ~ 40%), the vial/flask should be frozen in liquid nitrogen to ensure the cessation of the polymerisation. The reaction mixture should be subsequently diluted with IPA (if started with 4 mL IPA/DMAEA (50% *v/v*) add another 4 mL of IPA) while still keeping the vial in liquid nitrogen. After allowing the polymerisation mixture to thaw, IPA should be removed *via* flushing with nitrogen (avoid using air instead as this induces hydrolysis, read subsequent section) until the polymer becomes viscous. Precipitation in cold hexane 3 times will ensure the removal of monomer and side-products as evident by the disappearance of the monomer peaks in ^{1}H NMR and the low molecular weight material in SEC, respectively (Figures 4.11, 4.18, 4.20 and 4.22).

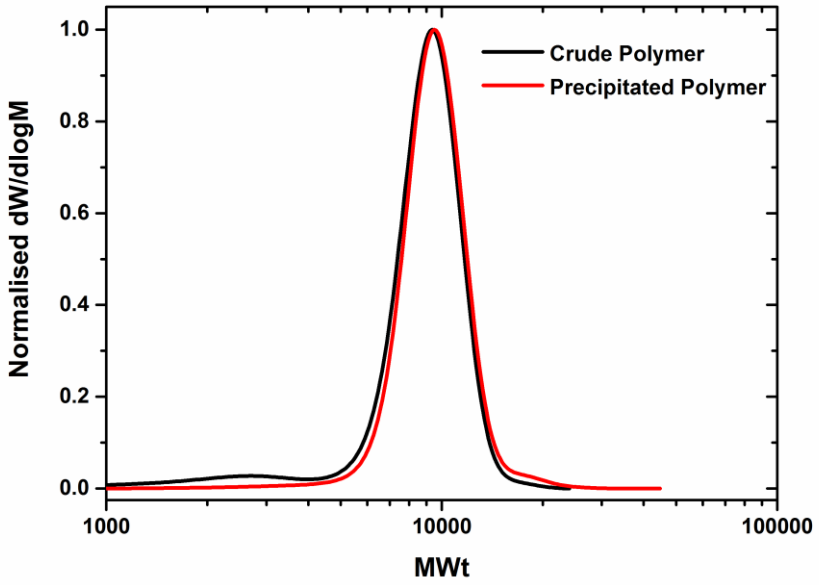
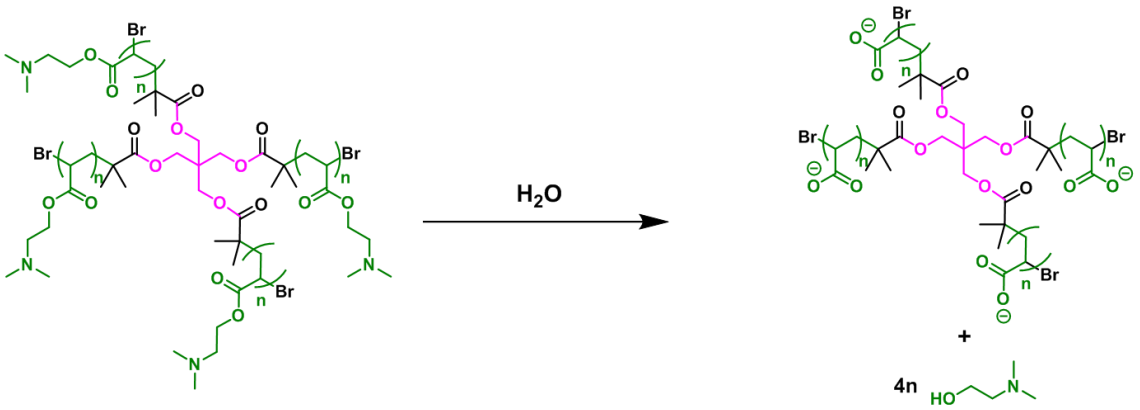


Figure 4.11: SEC data illustrating the effect of precipitation on the molecular weight distribution of 4-arm PDMAEA prepared in IPA.

Please note, the viscous polymer mixture should be added to hexane or vigorous shaking is required in the reverse scenario (addition of hexane to polymer) so to remove all monomer. During the precipitations a small amount of IPA can be used to collect the

precipitated polymer which can then be removed by flushing with nitrogen prior to the next precipitation.

4.2.6. Hydrolysis and Storage of PDMAEA stars



Scheme 4.4: PDMAEA hydrolysis to poly(acrylic acid) and dimethylaminoethanol.

As PDMAEA is known to hydrolyse to poly(acrylic acid) and N,N'-dimethylaminoethanol, (Scheme 4.4) the choice of the appropriate polymerisation solvent is crucial. In order to verify this, different solvents were screened to ascertain the degree of hydrolysis of PDMAEA including water (deuterium oxide), DMSO (deuterated), IPA, and chloroform ($CDCl_3$) (Table 4.8 and Figure 4.12). A PDMAEA star of $M_{n\,(SEC)}$ ~ 10500 was synthesised in IPA utilising a 4-arm initiator and isolated *via* purification (as described in previous section, reaction stopped at 48% conversion) with $Đ$ ~ 1.04. The purified polymer (24 mgs) was subsequently diluted with 0.6 mL of each solvent and the degree of hydrolysis was measured by ^{1}H NMR. Water revealed a significant amount of hydrolysis after 1 day (~ 36%). A further increase in the extent of hydrolysis was observed in more prolonged times, albeit with a much slower rate, with 73% hydrolysis after 4 weeks for water. Thus, water is an unsuitable solvent for the polymerisation of DMAEA. On the contrary, DMSO, $CHCl_3$ and IPA showed no hydrolysis, even after 30 days, which suggests that they are better candidates for the controlled polymerisation of DMAEA. However, $CHCl_3$ was not selected as the polymerisation solvent due to the potential of

this molecule to act as an initiator, in addition to the multi-functional initiator. As such, IPA was chosen as the ideal polymerisation solvent.

Table 4.8: ^{1}H NMR hydrolysis study performed in $CDCl_3$, D_2O, deuterated DMSO and isopropanol.[a]

Reaction Time (d)	Hydrolysis % $CDCl_3$	Hydrolysis % D_2O	Hydrolysis % DMSO	Hydrolysis % IPA
1	0	36	0	0
2	0	48	0	0
3	0	53	0	0
4	0	56	0	0
5	0	59	0	0
6	0	61	0	0
7	0	62	0	0
8	0	64	0	0
9	0	65	0	0
14	0	68	0	0
21	0	71	0	0
30	0	73	0	0

[a]These experiments were performed at 25 °C in a NMR tube. Conversions were calculated based on a comparison between CH_2 functionalities in the polymers and the small molecule 2-dimethylaminoethanol.

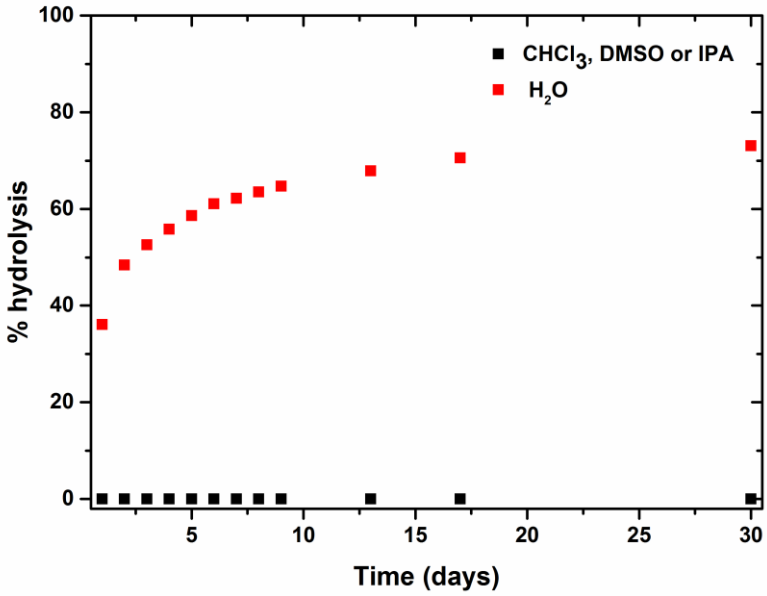


Figure 4.12: ^{1}H NMR hydrolysis study performed in $CDCl_3$, D_2O, deuterated DMSO and isopropanol.

Another interesting observation is the challenge in storing such materials. Once precipitated, the purified PDMAEA ($M_{n\,(SEC)}$ ~ 10000, $Đ$ ~ 1.08) was placed in a vial, and sealed with a cap. After 2 days, a small, yet visible, high molecular weight shoulder was

evident in the SEC with an observed increase in the dispersity from 1.08 to 1.15 ($M_{n\,(SEC)}$ = 10600). After one week the dispersity was further increased to 1.25 ($M_{n\,(SEC)}$ = 11900) while after 1 month multimodality was dominant revealing broad molecular weight distributions ($M_{n\,(SEC)}$ = 16200, $Đ$ ~ 3.57) (Figure 4.13a). Hence, it is evident that PDMAEA 4-arm stars cannot be efficiently stored in a vial, even when they are kept under a nitrogen atmosphere.

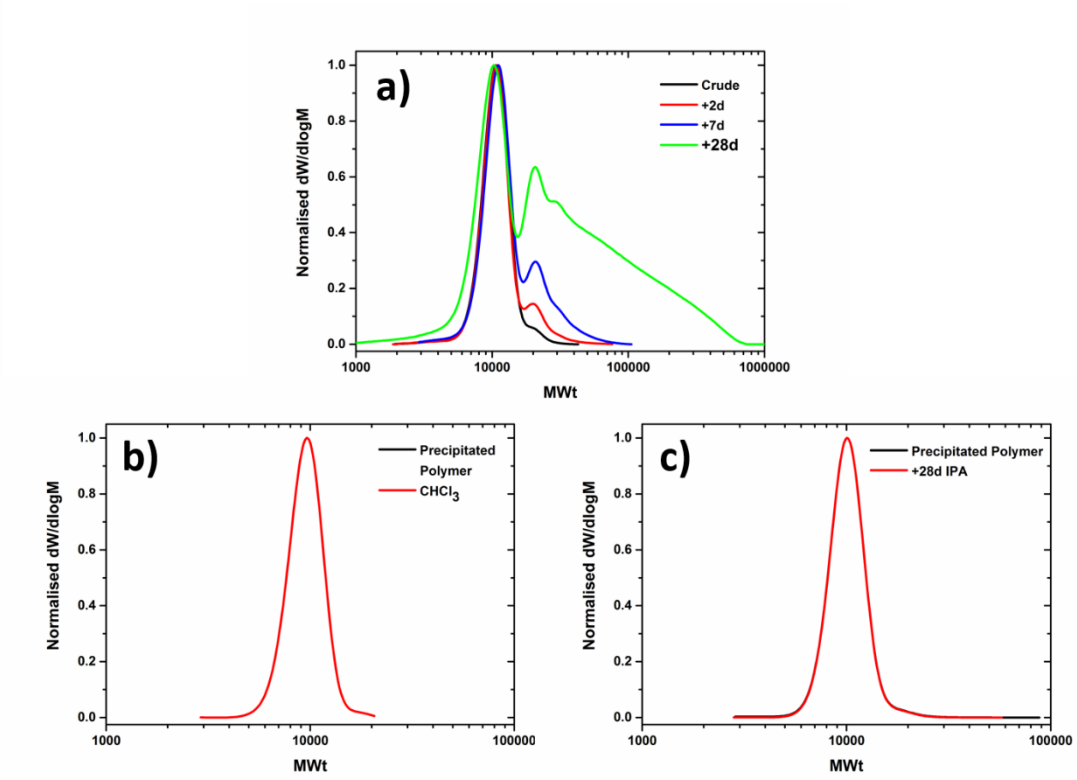


Figure 4.13: SEC traces illustrated the effect of storage of purified PDMAEA a) in a vial or via dilution in b) $CHCl_3$ or c) IPA.

As shown earlier during the hydrolysis study, both $CHCl_3$ and IPA showed negligible, if any, hydrolysis which suggests that both of the solvents could facilitate the successful safe storage of these materials (Figures 4.13b-c). In addition to that, both solvents have already demonstrated to efficiently terminate the polymerisation (by dilution as shown in previous section) and eliminate star-star coupling. As such, the purified PDMAEA 4-arm star ($M_{n\,(SEC)}$ ~ 10600, $Đ$ ~ 1.06) was stored separately in IPA and $CHCl_3$ for one month, after which period both samples were analysed by both NMR

and SEC. No sign of hydrolysis could be detected by NMR while neither low nor high molecular weight shoulders could be seen in the SEC chromatogram and the initially low dispersity ($Đ$ ~ 1.06) was maintained. Therefore, it was shown that both IPA and $CHCl_3$ can be used for the effective storage solvents for PDMAEA stars by preventing both termination and side reactions.

4.3. Conclusions

In summary, the synthesis of well-defined PDMAEA stars in a range of molecular weights ($M_{n\ (SEC)}$ ~ 5000-41000) was described. Cu(0)-RDRP using Cu(0) wire was successfully employed to control the polymerisation of DMAEA at ambient temperature. DMSO and IPA were investigated as reaction media, showing slightly different findings. The polymerisation in DMSO proceeded under purely homogeneous conditions in a controlled manner up to ~ 40% conversion with narrow molecular weight distributions attained ($Đ$ ~ 1.1). When the polymerisation was left to proceed for longer reaction times, high molecular weight shoulders were observed by SEC and the dispersity increased significantly ($Đ$ ~ 2). On the contrary, under heterogeneous conditions (IPA) less star-star coupling is observed while a low molecular weight shoulder appears, indicating terminated polymer chains at the earlier stage of the polymerisation, when the conversion exceeds 55%. Nevertheless, when the macroinitiator is isolated up to ~ 40% conversion, well defined block copolymers can be obtained ($M_{n\ (SEC)}$ ~ 20000, $Đ$ < 1.19), demonstrating that high end group fidelity can be maintained up when moderate conversions are targeted. Crucially, a detailed way of how to terminate and purify these materials is also presented by immediate dilution of the reaction mixture into either $CHCl_3$ or IPA which effectively stops the polymerisation. In addition, the storage of PDMAEA stars in these solvents could was also demonstrated, eliminating hydrolysis and preventing star-star coupling.

4.4. Experimental Part

4.4.1. Materials

All materials were purchased from Sigma Aldrich (Merck) or VWR and used as received unless otherwise stated. DMAEA was used as it is. Distillation of DMAEA or passing the monomer through a column of alumina had no effect on the subsequent polymerisation (data not shown). HPLC IPA (99.9%) was used for all the experiments, including the chain extensions and the storage studies. Methyl acrylate was passed through a basic Al_2O_3 chromatographic column prior to use to remove the inhibitor. *Tris*-(2-(dimethylamino)ethyl)amine (Me6Tren), *octa*-*O*-isobutyryl bromide lactose (8-arm initiator)[62] and 1,1,1,1-*tetra*(methyl-2-methyl-2-bromopropionate (4-arm initiator)[63] were synthesised according to previously reported literature. Cu(0) (gauge 0.25 mm) wire was purchased from Comax Engineered wires and purified by immersion in conc. HCl for 15 minutes, subsequently rinsed with water and dried prior to use.

4.4.2. Instrumentation

NMR spectra were recorded on Bruker DPX-300 or DPX-400 spectrometers in $CDCl_3$. Chemical shifts are given in ppm downfield from the internal standard tetramethylsilane. Monomer conversions were determined *via* ^{1}H NMR spectroscopy by comparing the integrals of monomeric vinyl protons to polymer signals. Size exclusion chromatography measurements were conducted using an Agilent 1260 GPC-MDS fitted with a differential refractive index (DRI) detector equipped with 2 PLgel 5 mm mixed-D columns (300 7.5 mm), 1 PLgel 5 mm guard column (50 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards ranging from 200 to 1.0 x10^6 g mol^{-1} were used as calibration standards. All samples were passed through a 0.45 mm PTFE filter prior to analysis. The mobile phase was chloroform with 2% triethylamine at a flow rate of 1.0

mL min^{-1}. SEC data were analysed using Agilent GPC/SEC software (version 1.2). MALDI-TOF-MS was conducted using a Bruker Daltonics Ultraflex II MALDI-TOF mass spectrometer, equipped with a nitrogen laser delivering 2 ns laser pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. Solutions in tetrahydrofuran (50 μL) of trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propyldene] malonitrile as a matrix (saturated solution), sodium iodide as the cationisation agent (1.0 mg mL^{-1}) and sample (1.0 mg mL^{-1}) were mixed, and 0.7 μL of the mixture was applied to the target plate. Spectra were recorded in reflector mode calibrating PEG-Me 1900 kDa. ICP-MS samples were analysed on an Agilent 7500cx ICP mass spectrometer in no-gas mode, with an average of 3 replicates with RSD below 1%. Copper calibration standards were prepared from QMX SCP28 multi-element mix to cover a range from 1 ppb to 1 ppm. Polymer samples were solubilised in 4% nitric acid solutions.

4.4.3. General Procedures

4.4.3.1. General Procedure for a Typical Cu(0)-RDRP of DMAEA using the 4-arm Initiator

DMAEA (2.65 mL or 2.50 grams, 140 equiv.), pre-activated copper wire (5 cm), 4-arm initiator (0.0915 grams, 1 equiv.), $CuBr_2$ (0.0112 grams, 0.40 equiv. with respect to the 4-arm initiator or 0.10 equiv. with respect to each initiating site/arm) and IPA (2.65 mL) were added to a septum sealed vial. The copper wire was carefully wrapped around the stirrer bar and the mixture was subsequently degassed by purging with nitrogen for 15 min. Me_6Tren (0.024 mL, 0.72 equiv. with respect to initiator or 0.18 equiv. with respect to each initiating site/arm) was then introduced in the vial *via* a gas-tight syringe and the polymerisation was allowed to commence at ambient temperature. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral

alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR. The reaction was terminated by dilution in IPA (another 2.65 mL) and the product was isolated *via* precipitation in cold hexane before being further characterised by NMR and SEC. An analogous procedure was followed when the 8-arm initiator was employed.

4.4.3.2. General Procedure for a Typical Chain Extension/Block Copolymerisation using the 4-arm Initiator

0.40 grams of the PDMAEA ($M_{n\,(SEC)}$ ~ 9100) macroinitiator was synthesised and isolated as described in the previous section and was subsequently dissolved in IPA (1.85 mL). 1.76 grams of MA (targeting DP = 464), 0.0039 grams of $CuBr_2$ (0.4 equiv. with respect to the macroinitiator), and 5 cm of copper wire (wrapped around a stirrer bar) were also included in the polymerisation mixture and the vial was sealed via a septum. The polymerisation mixture was then degassed by purging with nitrogen for 15 min and Me6Tren (0.008 mL, 0.72 equiv. with respect to the macroinitiator) was subsequently introduced in the vial and the polymerisation was allowed to commence at ambient temperature under a nitrogen blanket. The diblock copolymer P(DMAEA-*b*-MA) was stopped at ~ 58% of conversion and was isolated *via* precipitation in heptane (3 times), followed by analysis by both ^{1}H NMR and SEC.

4.5. Additional Characterisation

Table 4.9: Summary of kinetic data for the Cu(0)-RDRP of DMAEA in DMSO utilising the linear initiator (EBiB) under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.05]:[0.18].[a]

Time (h)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	Đ
0.5	24	4800	4900	1.26
1	31	6200	7300	1.24
2	44	8800	10300	1.25
3	51	10200	11000	1.33
4	57	11400	12400	1.35
5	62	12400	12600	1.50
14	73	14600	15600	1.75

[a]5 cm of Cu(0) wire, 5% $CuBr_2$ and 18% Me_6Tren with respect to initiator was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to DMSO was maintained at 1:1. The target molecular weight was 20000 g mol^{-1} and conversion was calculated via ^{1}H NMR.

Table 4.10: Summary of kinetic data for the Cu(0)-RDRP of DMAEA in DMSO utilising the linear initiator (EBiB) under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me6Tren]=[1]:[140]:[0.10]:[0.18].[a]

Entry	Time (h)	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	Đ
1	0.5	9	1800	1500	1.23
2	1	12	2400	2600	1.19
3	2	23	4600	4700	1.17
4	3	28	5600	6300	1.17
5	4	31	6200	7800	1.21
6	5	38	7600	9200	1.26
7	14	64	12800	15500	1.65

[a]5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me_6Tren with respect to initiator was utilised. Reactions were performed at 25 °C and the volume ratio of monomer to DMSO was maintained at 1:1. The target molecular weight was 20000 g mol^{-1} and conversion was calculated via ^{1}H NMR.

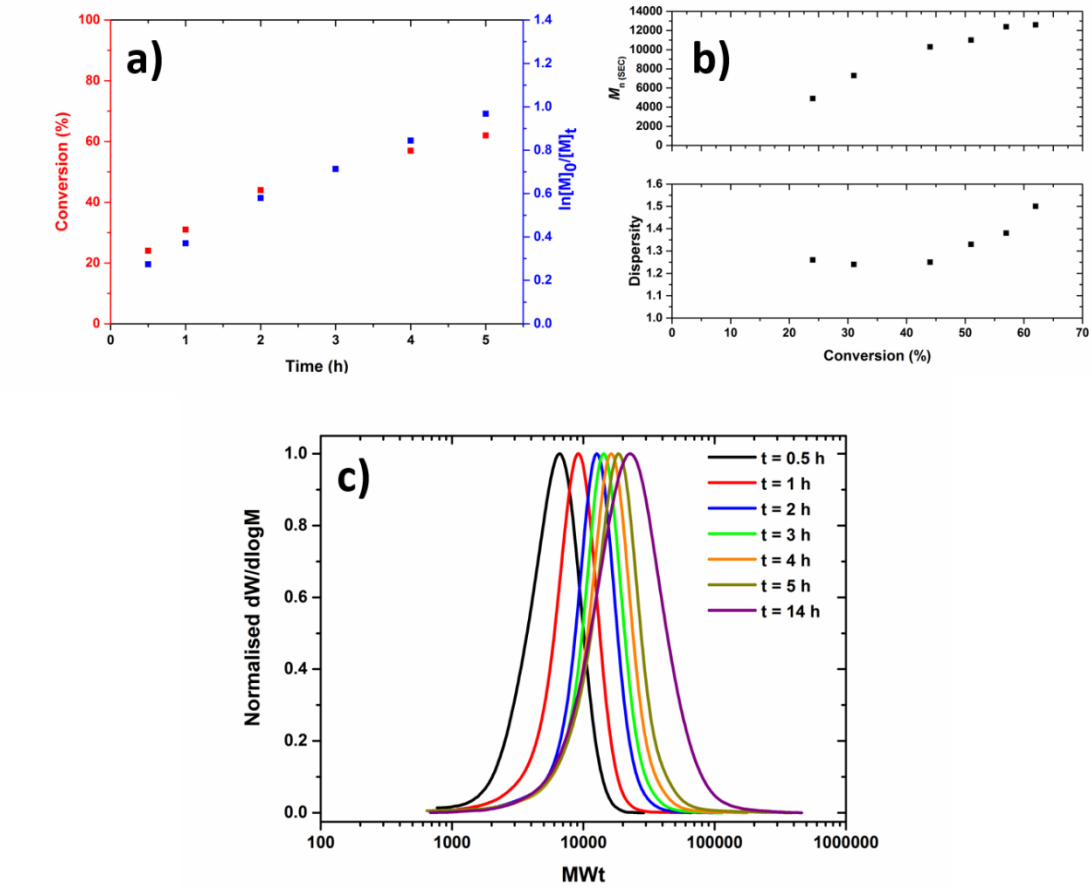


Figure 4.14: Kinetic and SEC data for the Cu(0)-RDRP of DMAEA in DMSO utilising the monofunctional EBiB initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.05]:[0.18]

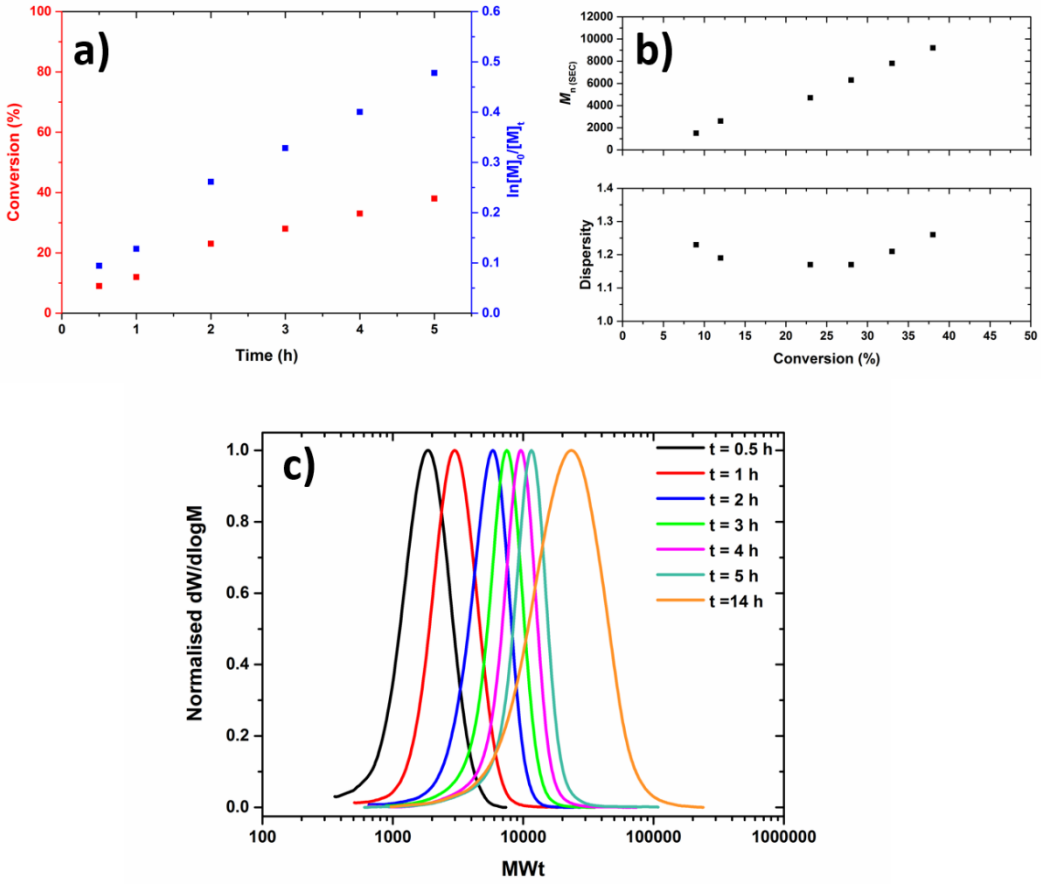


Figure 4.15: Kinetic and SEC data for the Cu(0)-RDRP of DMAEA in DMSO utilising the monofunctional EBiB initiator under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.10]:[0.18].

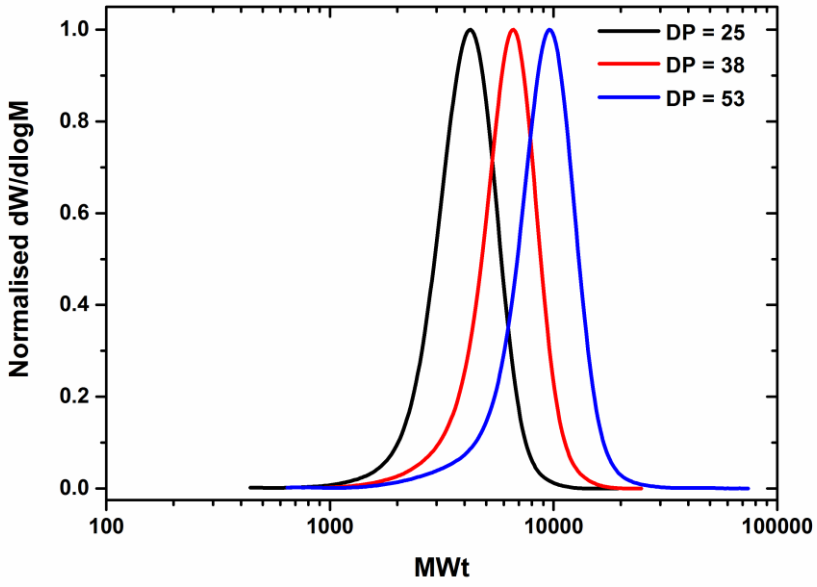


Figure 4.16*:* SEC analysis of PDMAEA with various DPs prepared via Cu(0)-RDRP in DMSO utilising a linear initiator, under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.10]:[0.18].

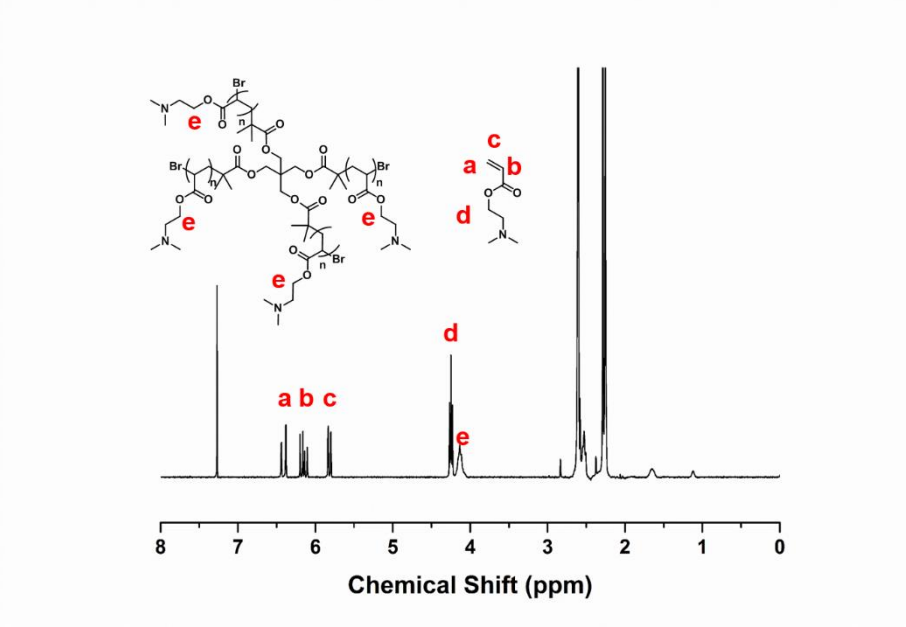


Figure 4.17: Typical crude ^{1}H NMR spectrum of 4-arm star PDMAEA in $CDCl_3$. Conversion is calculated by comparing the $–OCH_2$ peak at ~ 4.2 ppm with the vinyl protons at ~ 5.8-6.4 ppm.

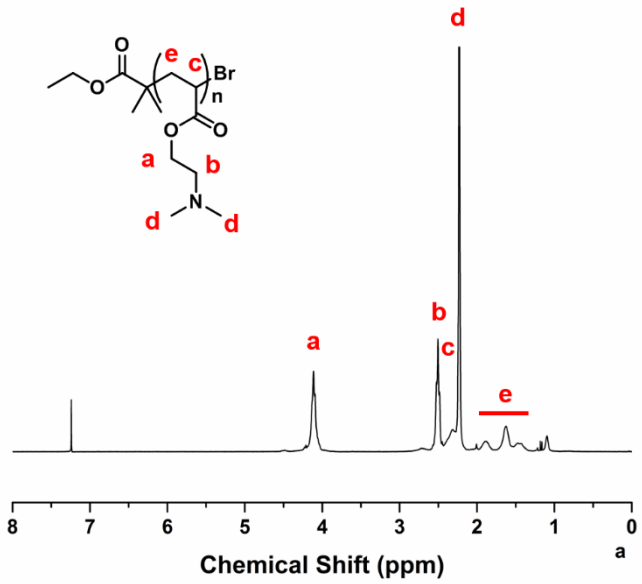


Figure 4.18: ^{1}H NMR of the purified linear PDMAEA in $CDCl_3$.

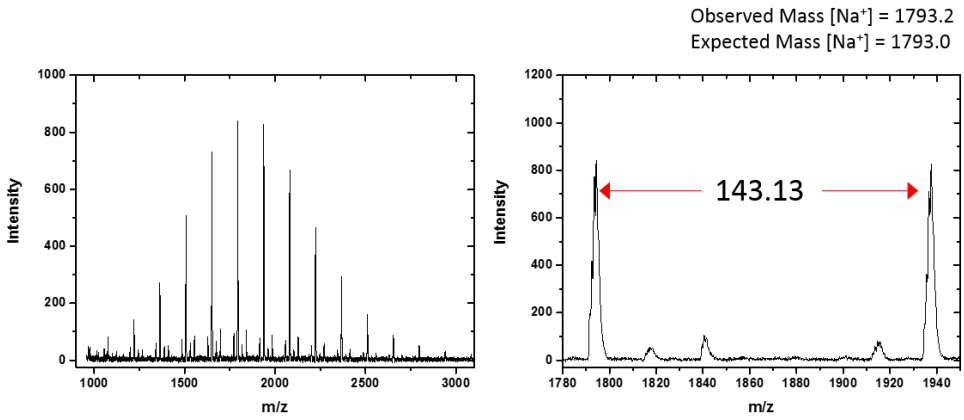


Figure 4.19: MALDI-ToF-MS spectra of bromine-terminated P(DMAEA) synthesised utilising the EBiB initiator, under the following reaction conditions [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.10]:[0.18].

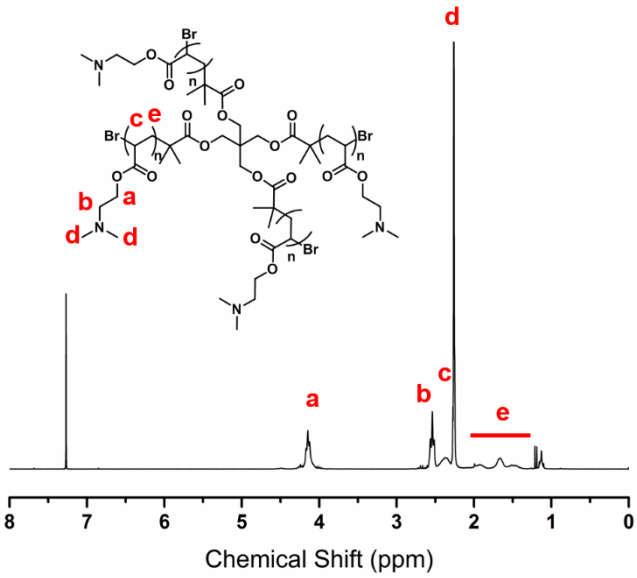


Figure 4.20: ^{1}H NMR of purified PDMAEA in $CDCl_3$ when a 4-arm initiator was used.

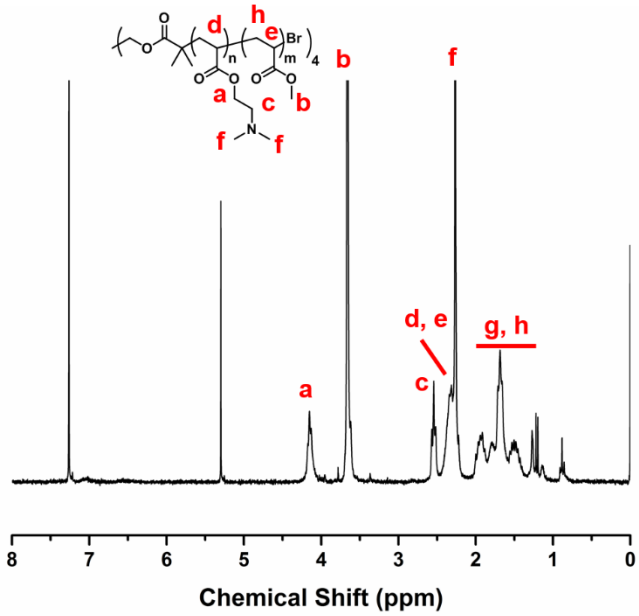


Figure 4.21: ^{1}H NMR of the purified block copolymer P(DMAEA-*b*-MA) in $CDCl_3$ utilising a 4-arm initiator.

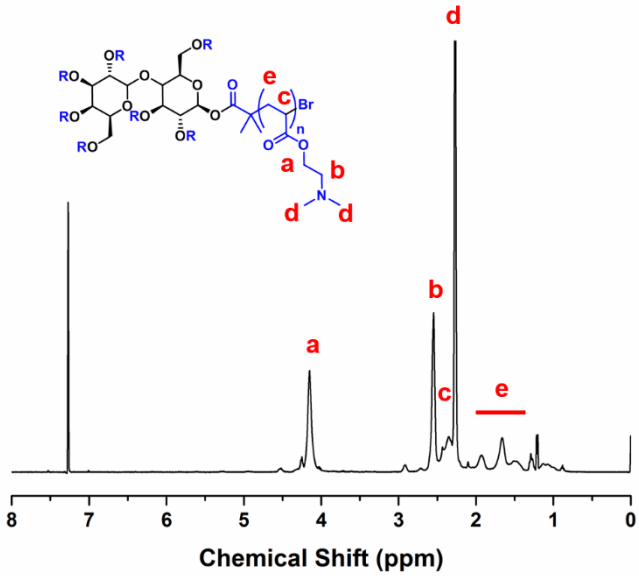


Figure 4.22: ^{1}H NMR of purified PDMAEA in $CDCl_3$ when a 8-arm initiator was used.

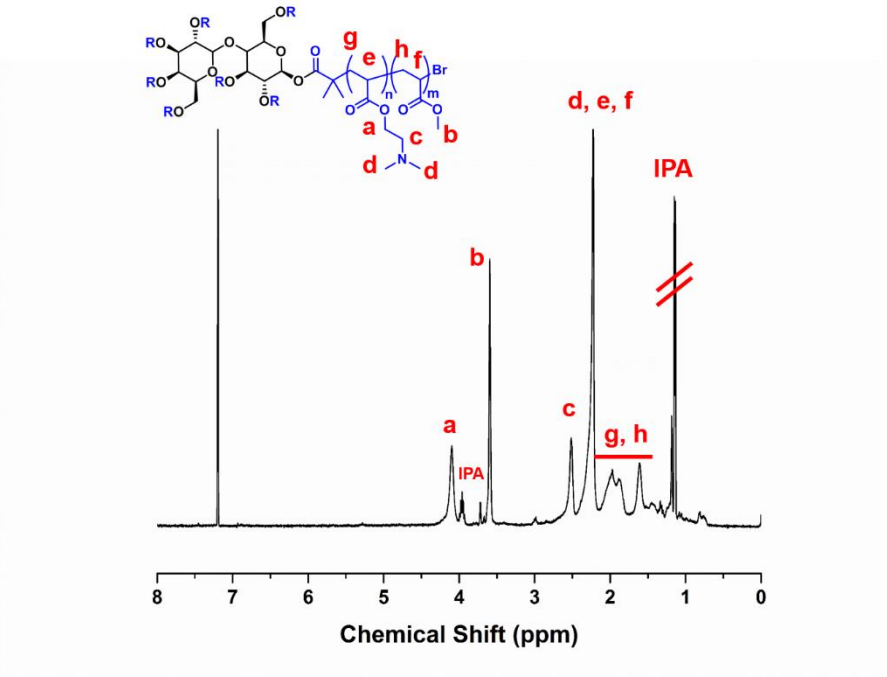


Figure 4.23: ^{1}H NMR of the purified block copolymer P(DMAEA-*b*-MA) in $CDCl_3$ utilising an 8-arm initiator.

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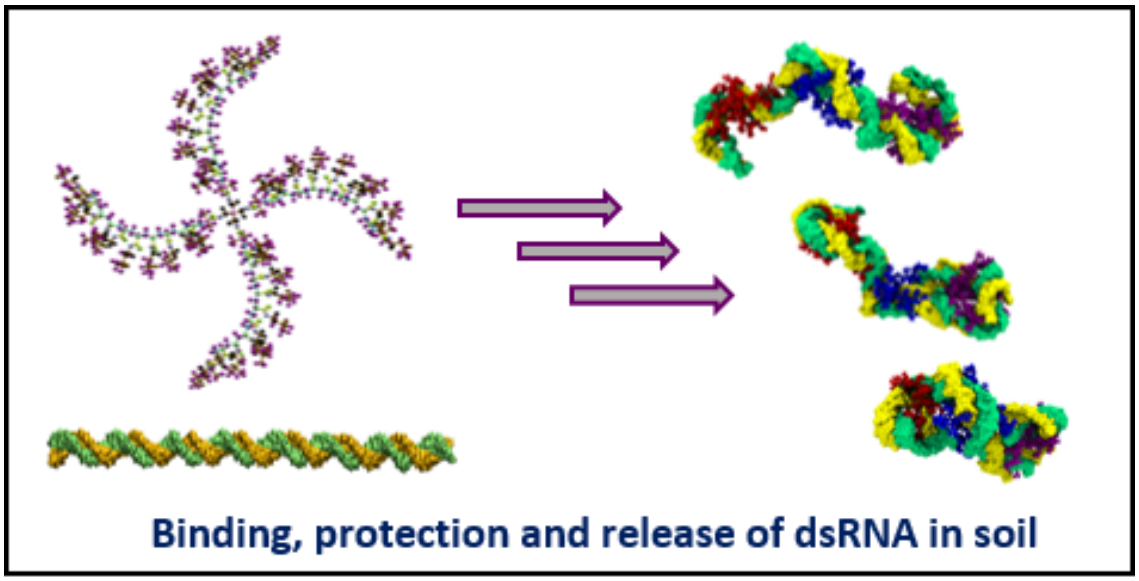
Chapter 5: Efficient Binding, Protection and Self-Release of dsRNA in Soil by Linear and Star Cationic Polymers



Double stranded RNA (dsRNA) exhibits severe degradation within three days in live soil limiting its potential application in crop protection. Herein we report the efficient binding, protection, and self-release of dsRNA in live soil through the usage of a cationic polymer. Soil stability assays show that linear poly(2-dimethylaminoethyl acrylate) can delay the degradation of dsRNA by up to one week while the star shaped analogue showed an increased stabilization of dsRNA by up to three weeks. Thus the architecture of the polymer can significantly affect the lifetime of dsRNA in soil. In addition, the hydrolysis and dsRNA binding and release profiles of these polymers were carefully evaluated and discussed. This creates great potential for many new opportunities in agrochemicals where protection and subsequent self-release of dsRNA in live soil is required.

This Chapter is adapted from *ACS Macro Lett*., 2018, ***7,*** 909–915.

5.1. Introduction

RNA interference (RNAi) is a naturally occurring process, where double stranded RNA (dsRNA) can regulate protein expression.[1-3] The use of dsRNA in the agrochemical industry is desirable as selected pests can be specifically targeted, whilst eliminating the detrimental effects of existing chemical pesticides on non-target species.[4] This technique is advantageous as an alternative method of chemical control to help mitigate the development of resistance by natural selection and also minimises potential environmental impact associated with current pest control methods.[5] However, the effectiveness of RNAi is limited by the very short lifetime of dsRNA which is susceptible to degradation under environmental conditions, with numerous pathways reported.[6] Ribonucleases (RNAses), for example are enzymes which degrade RNA into smaller fragments, and are not only found within the environment, but also in the air, dust and on surfaces. This inherent instability and short half-life of dsRNA when in contact with these enzymes represents a serious challenge in applying RNAi to agrochemicals.

Although most of the reports focus on delivering dsRNA to insects through microinjection into the haemolymph or feeding,[5, 7, 8] RNAi has also been shown to be effective in knocking down insect genes in plants, with delivery on to the surface of a leaf prior to insect feeding, or through in vivo dsRNA production within the chloroplast.[9-11] Nevertheless, all these methods are challenging for the application to large scale agrochemicals.[5, 12] A potential alternative route for delivering dsRNA to the plant could be via soil, followed by uptake through the roots, or ingestion by a pest. It has been illustrated that root cells can absorb dsRNA and RNAi can be triggered,[13, 14] however, applying this process to soil creates additional challenges as soil contains many chemicals (salts, minerals and nutrients), enzymes and living (micro)organisms, which can interact and vastly increase the rate of degradation of RNA.[15-17] A method of protecting dsRNA

and increasing lifetime in soil would be highly desirable, yet no efforts on stabilizing dsRNA in soil have been reported.

As mentioned in Section 1.5, cationic polymers have been extensively employed to protect RNA and DNA from degradation with numerous natural and synthetic examples [18, 19] including amine functionalised polysaccharides,[200] poly(L-lysine),[21] poly(amidoamines),[22] poly(amino-co-ester)s,[23, 24] poly(dimethylaminoethyl methacrylate) (PDMAEMA) [25] and poly(ethylene imines).[26] Although these polymers can efficiently bind to RNA they are however incapable of release due to the very high positive charge density. Release must occur to allow the dsRNA to become available so to trigger RNAi.[27] Considerable efforts have been directed at overcoming this problem, in particular, poly(2-dimethylaminoethyl acrylate) (PDMAEA) has been reported as having a self-catalysed hydrolysis property, with autodegradation to poly(acrylic acid) and 2-dimethylaminoethanol when in aqueous solution.[28-30] In addition, PDMAEA has a high transfection efficiency into HeLa cells when complexed with RNA, can facilitate complete release of RNA and exhibits very low toxicity.[27, 31-33] We thus envisaged that PDMAEA could be a good candidate to protect the dsRNA in soil and delay degradation prior to release.

In this chapter we study for the first time the use of a cationic polymer to increase the lifetime of dsRNA in soil. The effect of the polymer backbone (polyacrylate vs polymethacrylate),[34] polymer architecture (linear vs star), and the soil temperature on the rate of hydrolysis is thoroughly investigated and discussed.

5.2 Results and Discussion

5.2.1. Synthesis of PDMAEMA Linear Homopolymers and PDMAEA Linear and Star Homopolymers via Cu(0)-RDRP

The controlled polymerisation of DMAEA is reported to be challenging by all reversible deactivation radical polymerisation methods reported to date, mainly due to the high reactivity of the tertiary amine functionality that leads to a large extent of termination and side reactions.[35] In order to circumvent this, the polymerisations of DMAEA are usually stopped at low conversions (~30%) followed by purification and storage of the materials in IPA prior to further use. Using conditions illustrated in the previous chapter, the Cu(0)-RDRP[36] of both linear and star PDMAEA were attempted aiming for molecular weights in the range of 5000-6000 g mol^{-1}.[37,38] It is noted that high molecular weight analogues were not targeted as low molecular weight polymers (< 10000 g mol^{-1}) have been widely reported to exhibit enhanced solubility when complexed to genetic material and possess much lower toxicity.[27] As such, well defined linear ($M_{n\,(SEC)}$ = 5600, Đ = 1.18, Table 5.1, Entry 1 and Figure 5.1a) and star PDMAEA ($M_{n\,(SEC)}$ = 6200, Đ = 1.14, Table 5.1, Entry 2 and Figure 5.1b) were obtained exhibiting good agreement between the theoretical and experimental values and narrow molecular weight distributions.

Table 5.1: ^{1}H NMR and SEC analysis of linear and star PDMAEA prepared via Cu(0)-RDRP in IPA, under the following reaction conditions: [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.10]:[0.18] for linear PDMAEA and [I]:[DMAEA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.40]:[0.72] for star PDMAEA[a]

Entry	Architecture	Conversion (%)	$M_{n\,(Theo.)}$ (g mol^{-1})	$M_{n\,(SEC)}$	Đ
1	Linear	30	6200	5600	1.18
2	Star	32	7100	6200	1.14
3	Star	15	3600	3800	1.09

[a]In homopolymerisations 5 cm of Cu(0) wire, 10% $CuBr_2$ and 18% Me6Tren with respect to each initiating site were utilised. The volume ratio of monomer to solvent was maintained at 1:1. The target MWt was 20000 g mol^{-1} in all cases and conversion was calculated *via* ^{1}H NMR.

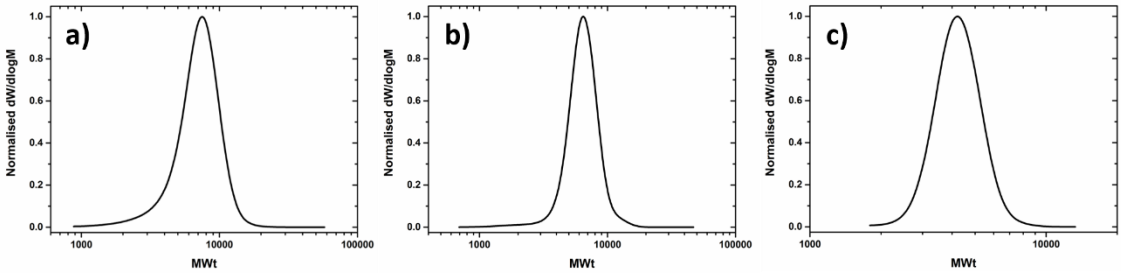


Figure 5.1: SEC analysis of a) linear and b-c) star PDMAEA prepared via Cu(0)-RDRP. The reactions a, b and c refer to Entries 1, 2 and 3 respectively in Table 5.1 respectively.

We also aimed to synthesise poly(2-dimethylaminoethyl methacrylate) the methacrylate analogue of PDMAEA, as it is a non-hydrolysable in aqueous solution so could be utilised as a negative control. The methacrylate cannot be used in soil applications, as this polymer does not provide a release mechanism for dsRNA.[25] It is worthy of note that reports of the synthesis of well-defined PDMAEMA are greater in number and this polymer can be stored as a white solid, with no evidenced storage or degradation issues. However, under identical conditions, the synthesis of PDMAEMA resulted in a broadening of the molecular weight distributions (Table 5.2, Entries 1-2 and Figure 5.2a).

Table 5.2: ^{1}H NMR and SEC analysis of linear PDMAEMA prepared via Cu(0)-RDRP in IPA, under the following reaction conditions: Entries 1 and 2) [I]:[DMAEMA]:[$CuBr_2$]:[Me_6Tren]=[1]:[140]:[0.10]:[0.18] (the analogous conditions to PDMAEA synthesis) and Entry 3) [MBPA]:[DMAEMA]:[$CuBr_2$]:[PMDETA]=[1]:[30]:[0.05]:[0.36].[a]

Entry	Target MWt (g mol^{-1})	Conversion (%)	$M_{n\ (Theo.)}$ (g mol^{-1})	$M_{n\ (SEC)}$	$Đ$
1	20000	36	7400	7200	1.33
2	20000	62	12600	13200	1.23
3	4200	>99.9	4200	6000	1.06

[a]The volume ratio of monomer to solvent was maintained at 1:1 and conversion was calculated *via* ^{1}H NMR.

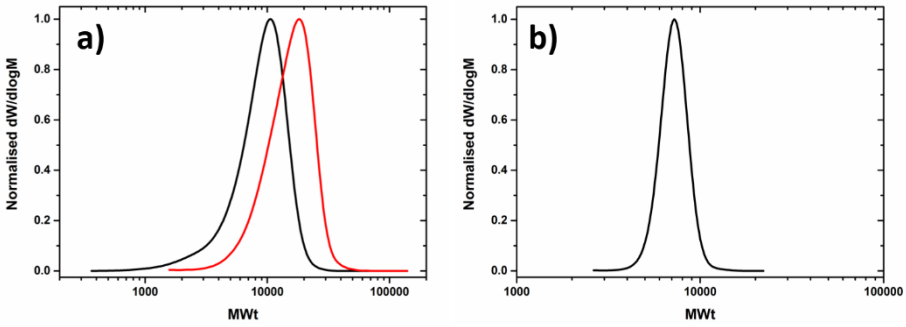
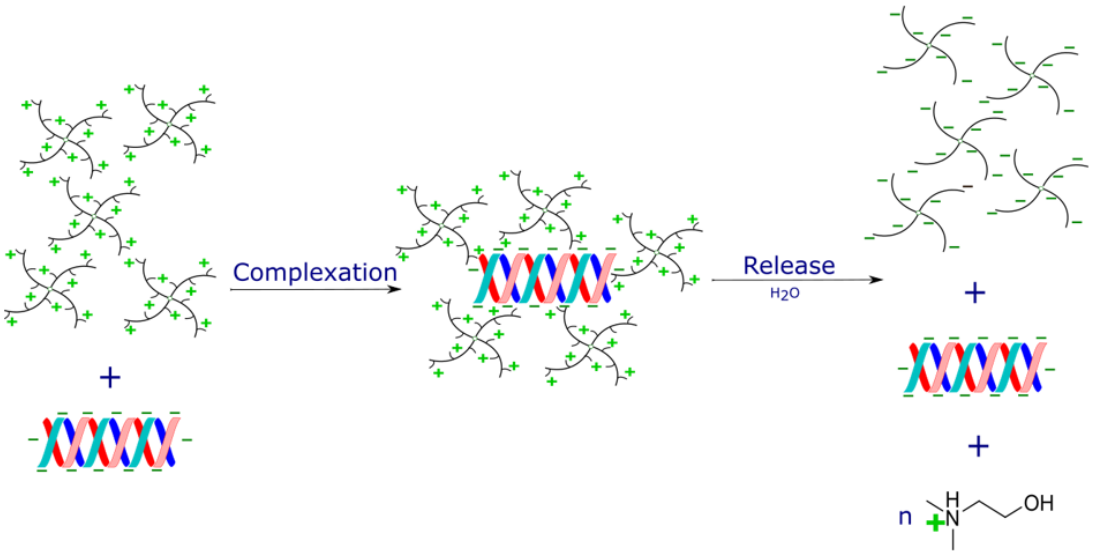


Figure 5.2: SEC analysis of PDMAEMA prepared via Cu(0)-RDRP. Figure 5.2a represents Entries 1 and 2 and Figure 5.2b represents Entry 3 in Table 5.2.

In order to circumvent this, MBPA and PMDETA (conditions that had been optimised in chapter 2) were instead utilised as the initiator and ligand respectively (as opposed to EBiB and Me_6Tren that were used for the linear acrylate polymers).[39] With this optimisation, well-defined linear PDMAEMA with low dispersity was obtained ($M_{n\,(SEC)}$ = 6000, Đ = 1.06). Importantly, this polymerisation reached full monomer conversion (>99% conversion by ^{1}H NMR) without compromising the molecular weight distribution (Table 5.2, Entry 3 and Figure 5.2a). To the best of our knowledge, this is the first illustration of the controlled polymerisation of DMAEMA via Cu(0)-wire RDRP.

5.2.1. The Effect of Polymer Structure and Environmental Conditions on the Rate of Hydrolysis



Scheme 5.1: The complexation of star PDMAEA to dsRNA, and subsequent release of dsRNA and the small molecule 2-dimethylaminoethanol.

All polymers (linear PDMAEA, linear PDMAEMA, star PDMAEA) were subsequently dissolved into aqueous solutions and the extent of the hydrolysis measured via ^{1}H NMR over 50 days (Table 5.3).[40] This prolonged time frame is necessary for potential soil applications and previous hydrolysis studies are limited to less than 10 days. The nature of the polymer backbone was initially investigated (methacrylate versus acrylate) with PDMAEMA showing negligible hydrolysis, if any, over the whole time (Table 5.3, Column 1 and Scheme 5.1) This is consistent with previous studies that report the methacrylate analogue to be non-hydrolysable, which is attributed to the greater hydrophobicity of the polymer backbone.[41] In contrast, upon switching from the polymethacrylate to the polyacrylate analogue (linear PDMAEA), hydrolysis occurred rapidly with 11% of the polymer being hydrolysed within 30 min, followed by a noticeable reduction in the degradation percentage with 25% of hydrolysis in 12 h and 50% in 3 days. The rate of hydrolysis was further decreased reaching 74% over the total period of 50 days (Table 5.3, Column 2 and Figure 5.3a). The mechanism of this reaction has yet to be published, but is likely to be due to a nucleophilic attack of the tertariy amine functionalities on the ester groups facilitated by water. Whether this reaction occurs within one monomer unit or between neighbouring monomer units on the polymer chain is yet to be determined and a study is currently underway to fully understand this mechanism.

Table 5.3: Results of the hydrolysis study comparing the hydrolysis profiles of PDMAEMA vs PDMAEA, Linear vs Star PDMAEA and two different molecular weights of star PDMAEA, all characterised by ^{1}H NMR.[a]

Reaction Time	Hydrolysis Linear PDMAEMA (%)	Hydrolysis Linear PDMAEA (%)	Hydrolysis Star PDMAEA (%)	Hydrolysis Low MWt Star PDMAEA (%)
0.5h	0	11	5	9
2h	0	14	9	12
4h	0	17	12	15
6h	0	19	15	18
8h	0	21	17	20
12h	0	25	22	24
1d	1	34	31	32
1.5d	1	42	39	38
2d	1	44	41	40
2.5d	1	47	45	43
3d	1	50	47	46
4d	1	54	50	49
5d	1	57	52	51
6d	1	59	55	53
7d	1	62	56	54
14d	2	67	62	63
21d	2	68	63	64
28d	2	71	65	66
35d	3	72	66	67
42d	3	73	68	69
49d	3	74	68	70

[a]All experiments were performed at 25 °C in a NMR tube. Conversions were calculated based on a comparison between CH_2 functionalities in the polymers and the small molecule 2-dimethylaminoethanol.

The hydrolysis study was then repeated for the star PDMAEA demonstrating also rapid hydrolysis with a slightly lower degradation percentage than for the linear analogue (Table 5.3, Column 3 and Figure 5.3a). It is noted that although the architecture seems to have only a small effect on the rate of hydrolysis, the linear polymers reproducibly hydrolyse slightly faster than the star polymers, possibly due to the greater density of cationic nitrogen moieties at the core of the star polymer that are less accessible to water molecules. In order to study the effect of small variations on the molecular weight within these materials, a lower molecular weight star polymer was also synthesised and tested ($M_{n\,(SEC)}$ = 3200, D = 1.12, Table 5.1, Entry 3 and Figure 5.1c). This experiment revealed

a similar rate of hydrolysis when compared to the higher molecular weight star polymer (63% versus 62%, Table 5.3, Column 4 and Figure 5.3b). Thus changing the molecular weight or the architecture has limited effect on the rate of hydrolysis This advantage allows the synthesis of PDMAEA with variable molecular weight from batch to batch, whilst maintaining the reproducible hydrolysis property that is needed for quality control.

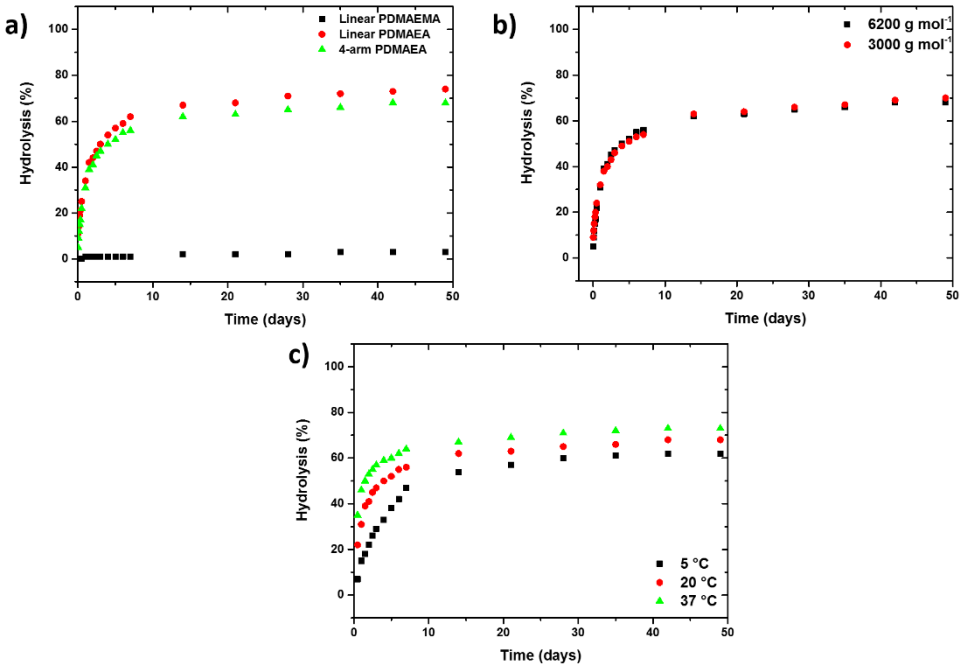


Figure 5.3: The effect of a) architecture b) molecular weight and c) temperature

Table 5.4: Results of the hydrolysis study comparing the effect of temperature on the rate of hydrolysis of PDMAEA, characterised by ^{1}H NMR.[a]

Reaction Time	Hydrolysis 5°C (%)	Hydrolysis 20°C (%)	Hydrolysis 37°C (%)
12h	7	22	35
1d	15	31	46
1.5d	18	39	50
2d	22	41	53
2.5d	26	45	55
3d	29	47	57
4d	33	50	59
5d	38	52	60
6d	42	55	62
7d	47	56	64
14d	54	62	67
21d	57	63	69
28d	60	65	71
35d	61	66	72
42d	62	68	73
49d	62	68	73

[a]All experiments were performed in a NMR tube. Conversions were calculated based on a comparison between CH_2 functionalities in the polymers and the small molecule 2-dimethylaminoethanol.

The next factor investigated was the effect of temperature on the degree of hydrolysis, with significant variations within different countries or different seasons. Hence, the hydrolysis at three different temperatures was tested (8, 20 and 37 °C, Table 5.5 and Figure 5.3d). The rate of hydrolysis slightly increased upon increasing the temperature, however, the difference in hydrolysis rate between 8 and 37 °C was only 4% at the end of the 50th day, thus showing relatively similar characteristics under significant temperature changes.

5.2.3. Binding and Release Studies of PDMAEA in Solution

To be applicable as a pesticide, dsRNA must bind and subsequently be released into the soil, so it can be absorbed by the plant root. With previous studies limited to the effect of a few polymer properties and environmental factors on the strength of complexation, we further investigated the effect of architecture on the rate of release utilising gel electrophoresis assays (Figures 5.4 and 5.5).[44-47]

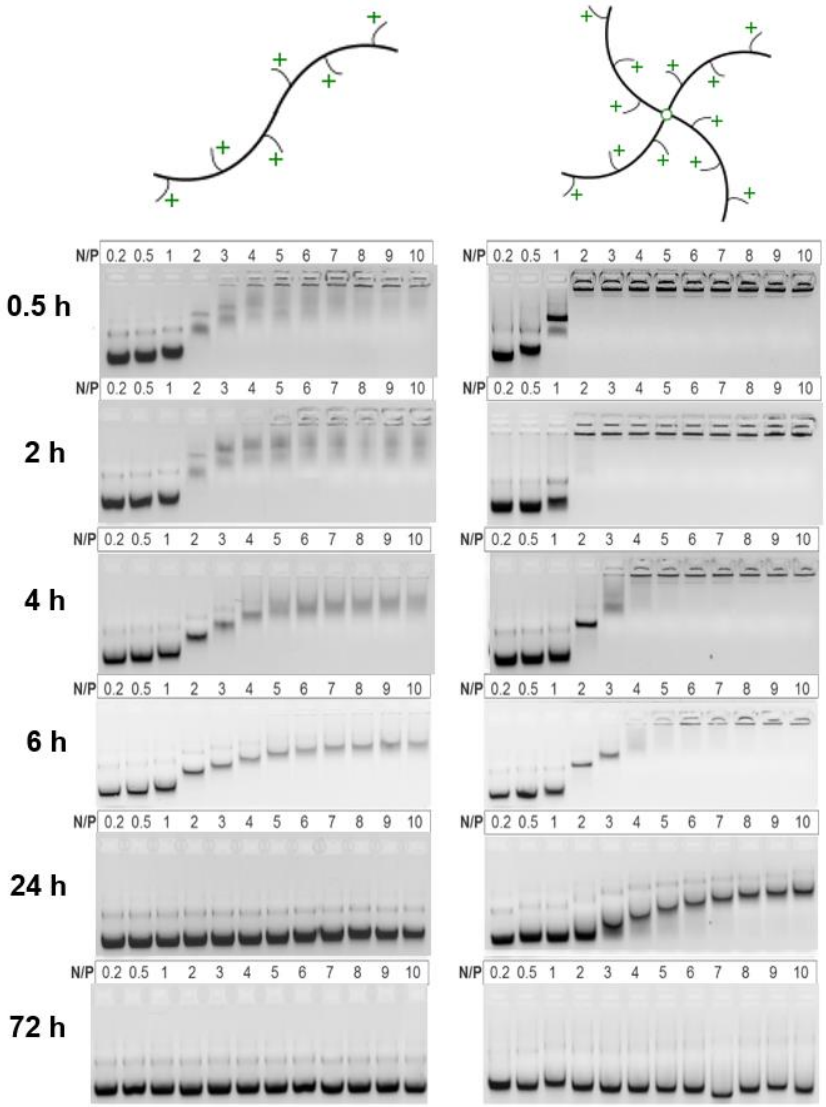


Figure 5.4: Gel retardation assay with dsRNA and linear/star PDMAEA. Polymer/dsRNA complexes were formed in RNase free water at increasing N+/P- ratio (0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) and evaluated after 0.5 hours, 2 hours, 4 hours, 6 hours, 24 hours and 72 hours. Polymer/dsRNA ratios are expressed as molar ratio between polymer ammonium (N+) cationic repeating units and the anionic phosphate groups (P-) on dsRNA. Samples were incubated at room temperature and loaded onto a 2% w/v agarose gel (100V, 30 minutes).

Polymer/dsRNA complexes (both linear and star) were incubated in RNase free water at increasing N^+/P^- ratios (0.2 to10). 0.5 h after incubation, the dsRNA remains loaded within the pockets of the gel, (the top band in Figures 5.4 and 5.5) indicating strong complexation between all polymers (linear PDMAEA, linear PDMAEMA, star PDMAEA) and dsRNA at an N^+/P^- ratio of 2 or greater. In comparison to the linear polymer, the star PDMAEA illustrated much more complete binding, as shown by dark

top band and no smearing in Figure 5.4 (right). At lower N^+/P^- ratios full binding did not take place as there were insufficient positive charges to bind all of the dsRNA, illustrated by the free dsRNA migrating through the gel. We next examined the ability of these complexes to release dsRNA, as only free dsRNA can be active and most complexes cannot self-release the dsRNA. As expected, the non-hydrolysable PDMAEMA exhibited no release of dsRNA even after 21 days as no noticeable change in the gel electrophoresis assay was observed (Figure 5.5).

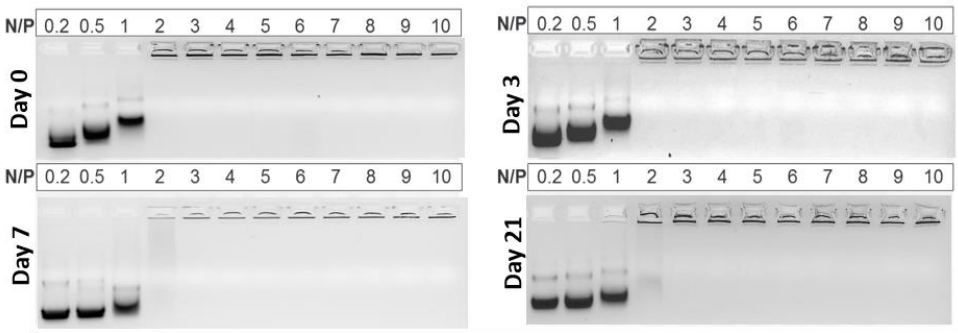


Figure 5.5: Gel retardation assay with dsRNA and linear PDMAEMA. Polymer/dsRNA complexes were formed in RNase free water at increasing N+/P- ratio (0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10) and evaluated after 30 minutes (day 0) , 3 days, 7 days and 21 days. Polymer/dsRNA ratios are expressed as molar ratio between polymer ammonium (N+) cationic repeating units and the anionic phosphate groups (P-) on dsRNA. Samples were incubated at room temperature and loaded onto a 2% w/v agarose gel (100V, 30 minutes).

On the contrary, for linear PDMAEA, smearing could be observed for all N^+/P^- ratios after 30 minutes (Figure 5.4 left) suggesting that binding had occurred, and that the partial release had already begun. It is not possible to gain an earlier measurement, as 30 minutes is the time taken to acquire a gel. This is in contrast to the star PDMAEA, which showed no release until after 4 hours for N^+/P^- ratios at 4 or greater. Taken altogether this data demonstrates that the star polymer has a much slower release profile than the linear analogue, with the nearly full release of the dsRNA having occurred for the linear polymer after 24 hours, but still some level of binding for the star polymer was evident.

Detailed binding and conformation changes of dsRNA-PDMAEA complexation were subsequently investigated using all-atom molecular dynamics (MD) simulation

(Figure 5.6). Previous reports have shown that the presence of cationic functionalised nanoparticles result in significant bending of DNA.[48]

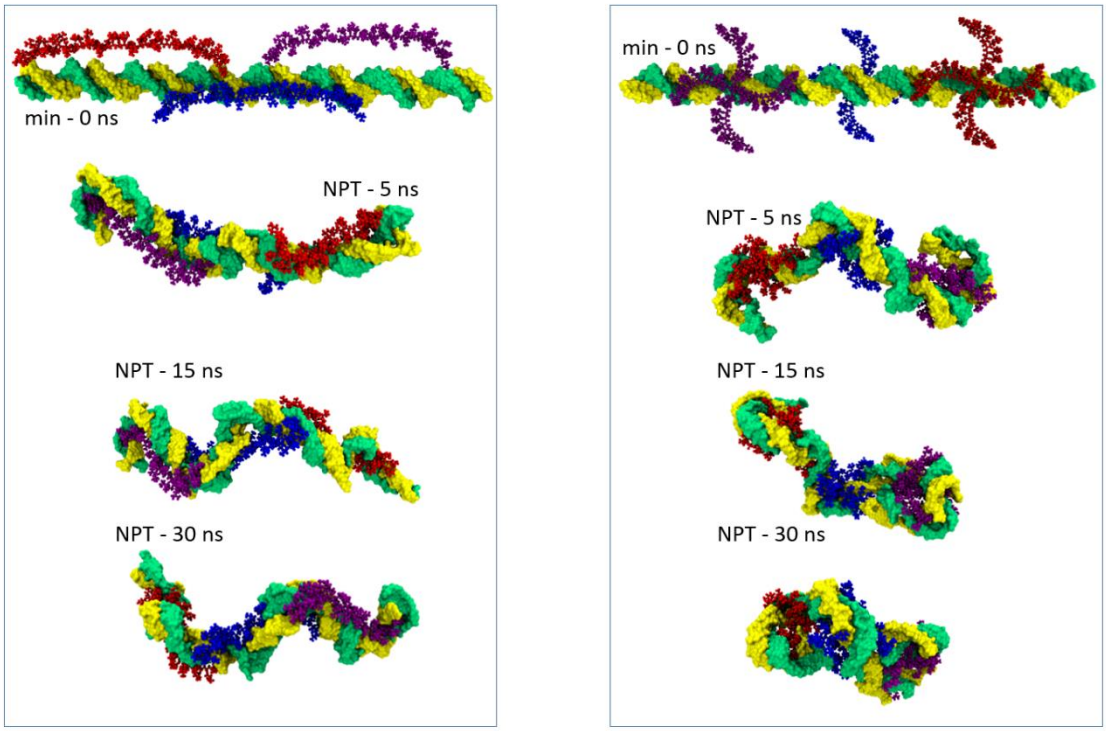


Figure 5.6: MD simulation snapshots of DNA/PDMAEA complexation for both linear and star polymer during various stages of wrapping process. Simulation shows significant bending of the double helix with the star polymer complex. DNA and polymers are shown in the surface representation in VMD: green and yellow are dsRNA, red, blue and purple are polymers.

However, there is currently no comprehensive study on the binding of cationic polymers of different architecture to dsDNA. In our simulation, both linear and star PDMAEA (DP40) are strongly bound to the dsDNA and had a profound impact on DNA conformation. The star polymer, however, is more effective in bending and wrapping itself around the dsDNA than its linear counterpart, thus a more compact DNA/polymer complex is formed. This is consistent with the gel electrophoresis data, as there is a lower surface area that can potentially come into contact with water or RNases, so better protection and slower release are illustrated.

Another important observation from the gel electrophoresis data, was that the N^+/P^- ratio has a significant effect on the rate of release with increasing the amount of

polymer resulting in a much slower rate. Full release of dsRNA is a desired attribute for cationic polymers and is illustrated for all N^+/P^- ratios of both the linear and the star PDMAEA.

5.2.4. Binding and Release Studies of PDMAEA in Soil

These polymers are therefore potentially good candidates for soil stability studies, so polyplexes formed from both the linear and star cationic polymers (N^+/P^- ratios of 5) were subsequently investigated (Figure 5.7). Soil stability assays were conducted by adding samples of polyplex to either live soil or baked soil, with samples incubated for up to 21 days. At each selected timepoint, TRI Reagent® (a mixture of phenol and guanidine thiocyanate) was added which inhibits any RNase activity, preventing subsequent degradation of dsRNA. This also facilitates the extraction of dsRNA from the soil and importantly separation from DNA and proteins. On the addition of chloroform followed by centrifugation 3 phases are formed: an aqueous phase containing RNA, an interphase containing DNA and an organic phase containing proteins.[49] Subsequent enrichment utilising a lithium chloride procedure allowed for analysis via gel electrophoresis.[50]

Initially, some important control experiments were conducted. In the absence of soil (RNase free solution) the naked dsRNA, the linear PDMAEA/dsRNA complex and the star PDMAEA/dsRNA complex showed no degradation of dsRNA. This is to be expected as in the absence of soil there are no bacteria or enzymes to facilitate degradation. In contrast, when the naked dsRNA was tested in live soil, the intensity of the dsRNA band was greatly reduced after 3 days, suggesting severe degradation of dsRNA. Conversely, when the linear PDMAEA was complexed to the dsRNA in the live soil, distinct bands could be observed after 3 and 7 days thus clearly showing that

complexation to linear PDMAEA was delaying the degradation of dsRNA in soil for around 4 days. However after 10 days the dsRNA was completely degraded.

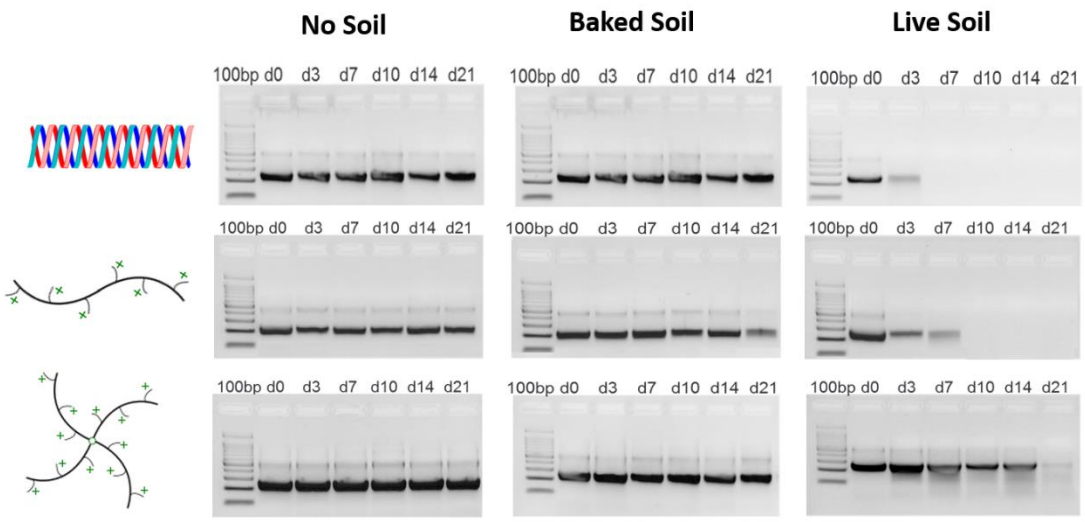


Figure 5.7: Evaluation of a) naked dsRNA b) linear PDMAEA/dsRNA complex and c) star PDMAEA dsRNA complex (200µL) in no soil, baked soil and live soil (0.5g). All polymer/dsRNA complexes were formed incubated at room temperature for different time periods (d = day 0, 3, 7, 10, 14, 21). dsRNA was extracted from soil and samples loaded onto a 2% w/v agarose gel (100V, 30 minutes) for subsequent analysis.

Remarkably, when the star PDMAEA was complexed to the dsRNA in live soil the degradation was further delayed with a strong band being observed even after 14 days while a much weaker band could still be observed even after 21 days. A further control experiment was undertaken, with the naked dsRNA, the linear PDMAEA/dsRNA complex and the star PDMAEA/dsRNA complex being tested in soil prebaked at 240°C. Having stopped the activity of bacteria and enzymes, no degradation took place confirming that indeed these organisms/enzymes are the only factor responsible for the live soil degradation. As such, it can be concluded that both linear and star PDMAEA can efficiently protect from dsRNA from degradation and extend the lifetime, but importantly the star/dsRNA complex exhibits significantly longer protection timeframes when compared to the linear analogue. This is attributed to the greater density of cationic functionalities within the core of the star polymer, resulting in more and stronger bonding with the dsRNA, hence a greater amount of hydrolysis is required for the release to occur.

5.3. Conclusions

In summary, PDMAEA has been illustrated to be a successful polymer for the effective binding and self-release of dsRNA in soil. Both linear and star PDMAEA were successfully synthesised via Cu(0)-RDRP, and the hydrolysis profile of these materials subsequently analysed. Interestingly the architecture was shown to have a significant effect on binding and release, with the star showing a much slower release rate in comparison to the linear polymer. When applied to soil, star PDMAEA protected dsRNA illustrating a significantly greater stabilisation time of 3 weeks compared to naked dsRNA which degraded after 3 days. The enhanced stability of dsRNA in soil by complexation to these polymers, followed by a unique self-release mechanism creates many new opportunities for using RNA interference in agrochemical applications.

5.4. Experimental Part

5.4.1. Materials

All materials were purchased from Sigma Aldrich (Merck) or VWR and used as received unless otherwise stated. 2-dimethylaminoethyl acrylate and 2-dimethylaminoethyl methacrylate were used as provided. HPLC IPA (99.9%) was used for all the experiments, including the chain extensions and the storage studies. Me_6Tren and 1,1,1,1-*tetra*(methyl-2-methyl-2-bromopropionate (star initiator) were synthesised according to previously reported literature.[1, 2] PMDETA was distilled prior to use. Cu(0) (gauge 0.25 mm) wire was purchased from Comax Engineered wires and purified by immersion in conc. HCl for 15 minutes, subsequently rinsed with water and dried prior to use.

Double stranded RNA (dsRNA) with ~ 152 base pairs was custom synthesised by in vitro transcription (Genolution, Korea) followed by a purification step using LiCl precipitation. All the experiments involving dsRNA were performed in deionised RNase free water. Polymer/dsRNA ratios are expressed as molar ratio between polymer ammonium (N+) cationic repeating units and the anionic phosphate groups (P-) on dsRNA. Live soil of composition: 51% sand, 24% silt and 25% clay, was provided dried and sieved through a 2mm sieve. Baked soil was live soil exposed to a temperature of 240°C for 2 hours.

5.4.2. Instrumentation

NMR spectra were recorded on Bruker DPX-300 or DPX-400 spectrometers in $CDCl_3$. Chemical shifts are given in ppm downfield from the internal standard tetramethylsilane. Monomer conversions were determined via ^{1}H NMR spectroscopy by comparing the integrals of monomeric vinyl protons to polymer signals. Size exclusion chromatography measurements were conducted using an Agilent 1260 GPC-MDS fitted with a differential refractive index detector equipped with 2 PLgel 5 mm mixed-D columns (300 7.5 mm),

1 PLgel 5 mm guard column (50 7.5 mm) and autosampler. Narrow linear poly(methyl methacrylate) standards ranging from 200 to 1.0 $x10^6$ g mol^{-1} were used as calibration standards. All samples were passed through a 0.45 mm PTFE filter prior to analysis. The mobile phase was chloroform with 2% triethylamine at a flow rate of 1.0 mL min^{-1}. SEC data were analysed using Agilent GPC/SEC software (version 1.2).

5.4.3. General Procedures

5.4.3.1. General procedure for a typical Cu(0)-RDRP of DMAEMA

Dimethylaminoethyl methacrylate (6 mL or 5.59 g, 30 equiv.), pre-activated copper wire (5 cm), methyl-α-bromophenylacetate (0.119 mL or 0.272 g, 1 equiv.), $CuBr_2$ (13.3 mg, 0.05 equiv.) and IPA (6 mL) were added to a septum sealed vial, equipped with a stirring bar, around which the copper wire was wrapped. The mixture was subsequently deoxygenated by bubbling with nitrogen for 20 min. PMDETA (0.089 mL, 0.36 equiv.) was then introduced in the vial via a gas-tight syringe and the polymerisation was allowed to commence at 40 ˚C for 18 h. Samples were taken periodically under a nitrogen blanket and passed through a short column of neutral alumina to remove dissolved copper salts prior to analysis by ^{1}H NMR and SEC.

5.4.3.2. General procedure for the hydrolysis of PDMAEA

PDMAEA (40 mg) was dissolved in D_2O (0.75 mL) and then transferred into an NMR tube. ^{1}H NMR measurements were taken at selected time intervals at room temperature. The percentage of hydrolysis that had occurred was calculated by comparing the integrals of the CH_2 peaks at 3.7 and 4.2 ppm respectively. Hydrolysis studies were further carried out at 5°C (in the fridge), and also at 25°C and 37°C (Herp Nursery II incubator).

5.4.4. dsRNA binding and release analysis

5.4.4.1. dsRNA/Polymer Complex Formation

Purified dsRNA was dissolved in RNase free water to achieve a stock solution of 2mg/ml. Polymer/dsRNA complexes were prepared by mixing polymer and dsRNA solutions at different molar ratios between polymer ammonium cationic repeating units and the anionic phosphate groups on dsRNA (N+/P- ratios) from 0.2 to 10. In this experiment, the final concentration of dsRNA was kept constant at 0.2 mg/ml whilst the polymer amount was varied to achieve the desired N+/P- ratio. After mixing the polymer and dsRNA solutions, the samples were vortexed and allowed to stand for 30 minutes prior to analysis.

5.4.4.2. Monitoring the Binding and Release of dsRNA *via* Gel Retardation Assay

The dsRNA/polymer mixtures described above were analysed by a gel retardation assay to determine the degree of dsRNA/polymer complexation and release. 10 µl samples of all polymer/dsRNA complexes with differing N+/P- ratios were loaded into separate wells of a 2% w/v agarose gel containing 0.5 µg/ml ethidium bromide. Electrophoresis was performed for 30 minutes at 100V and the gel visualised under UV light using a transilluminator.

5.4.4.3. Soil Stability Assay Overview

200 µl samples of 1 mg/ml i) naked dsRNA and ii) dsRNA complexed with polymers at N+/P- ratio of 5, were transferred into Eppendorf tubes containing either 0.5 g of live soil or 0.5 g of baked soil. Samples were incubated at 24 ^{o}C for up to 21 days in separate tubes for each time point to be assessed (days 0, 3, 7, 10, 14 and 21). 1 ml of TRI Reagent® was added to a tube after each time point was reached, the sample was vortexed until homogeneous and allowed to stand at room temperature for 5 minutes. The samples were

then stored at -20°C until the end of the experiment (day 21), after which they were defrosted.

5.4.4.4. dsRNA Soil Extraction Procedure

200 µl of chloroform was added to each defrosted sample, which were subsequently vortexed and left to stand for 3 minutes at ambient temperature. The samples were centrifuged for 15 minutes at 12000 g at 4°C and 400 µl of supernatant was transferred to a new Eppendorf tube. Isopropanol (1:1 v/v ratio) was added and the samples were allowed to stand for 10 minutes at room temperature. The samples were centrifuged for 10 minutes at 12000g at 4°C, the supernatant was removed and the pellet washed with 500 µl of 70% ethanol. Each pellet was resuspended in 200 µl RNase free water and 67 µl of 8M LiCl was added. Samples were exposed to a temperature of -20 ^{o}C for 30 minutes and subsequently centrifuged for further 20 minutes at 17000g at 4°C. The supernatant was transferred to a new eppendorf tube and 133.5 µl of 8M LiCl was added to achieve a final concentration of 4M LiCl. The samples were stored overnight at -20°C, centrifuged for 20 minutes at 17000g at 4°C and the supernatant removed. Each sample was washed with 150 µl 70% ethanol and the pellet re-suspended in 20 µl of RNase free water.

5.4.4.5. dsRNA Degradation Assessment Procedure

The dsRNA samples were loaded on a 2% w/v agarose gel in presence of ethidium bromide (max. 2ug dsRNA loading per well) and electrophoresis performed for 30 minutes at 100V. The gel was visualised under UV light using a transilluminator**.**

5.4.5. Simulation Details

All-atom molecular dynamics simulations were driven by LAMMPS software package with CHARMM27 force field for dsDNA. PDMAEA polymers were modelled using the all-atom Optimised Potential for Liquid Simulations (OPLS/AA) force field. The

extended simple point charge (SPCE) model was used for water. Lorentz-Berthelot mixing rules, which estimate intermolecular potential parameters of the Lennard-Jones potential using an arithmetic average for the collision diameter and a geometric average for the well depth, were used to supply the missing Lennard-Jones parameters. This Lorentz-Berthelot mixing rule was reported working well when the dominance interactions are electrostatic.[3]

R package was used to generate a random DNA sequence of 76 base pairs, which includes 27A, 18C, 21T and 10G, as follow: ATAATCTATACAGGCGGTGTCACTAATAGAGT TAGCATTTTAAGTTAACCTATCAAATAATCACAACCGTCCCACC. The initial DNA and polymers structures were built with MOLTEMPLATE. The linear polymer chain is made of 40 fully protonated DMAEA units, while the star polymer have 4 arms and each of them carries 10 fully protonated DMAEA units. For simulations of DNA/polymer binding, 3 polymer chains of either linear or star shape were initially placed along the DNA and with a centre of mass distance of approximately 3 nm from the DNA. Polymer-DNA systems were placed in simulation boxes of dimension 110×300×100 Å to ensure the absence of periodic image interactions and solvated with 45000 water molecules with the PACKMOL tool. The simulations were run on TINAROO cluster (The University of Queensland's Research Computing Centre) with a time step of 1 fs. The particle-particle particle-mesh (PPPM) method with an RMS accuracy of 10^{-4} was used to treat the long-ranged electrostatic and van der Waals interactions. The SPCE water molecules were constrained in bond lengths and the angles by the SHAKE algorithm. The energy of the packed system was minimised using the steepest descent and conjugate gradient algorithm for a total 100000 steps. The simulation was continued with the NPT ensemble at 1 bar pressure and temperature of 298 K

employing the Nose-Hoover thermalstat and barostat with a relaxation time up to 1000 fs. The energy and density fluctuations were monitored every 50 fs and the trajectory was recorded every 2000 fs.

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Chapter 6: Conclusions

This thesis utilises Cu(0)-RDRP as a methodology to synthesise a range of polymeric materials, exhibiting narrow molecular weight distributions in all cases. There are two main challenges which are overcome, firstly the polymerisation of low k_p hydrophobic monomers and secondly the synthesis of well-defined cationic polymers, which were then applied to applications in soil.

Cu(0)-RDRP is a multicomponent system, which typically requires optimisation of a number of components. In Chapter 2, one set of conditions were utilised to polymerise polyacrylates, polymethacrylates and polystyrene, in all cases yielding polymeric materials with narrow dispersities at near quantitative conversions. High end group fidelity was achieved for all three of the polymer classes, so a range of block copolymers could be synthesised with no loss of control over the polymerisation while maintaining dispersities of less than 1.20. By utilising a high activity initiator, carefully selecting a solvent that can yield well-defined polymers in both homogeneous and biphasic polymerisation systems and only utilising commercially available and inexpensive reagents, this one set of conditions allows facile access to three broadly applicable polymer classes for all researchers.

However, compromises over conditions for the polymerisation of each monomer class were sought so to maintain control for all three polymerisation systems, in particular for the polymerisation of styrene a limited molecular weight (~ 15000 g mol^{-1}) was achieved and initiator efficiencies were limited. The synthesis of polystyrene is particularly limited in the literature also, so in Chapter 3 a number of optimised conditions were developed. Three solutions were achieved, namely increasing the ligand concentration, changing the initiator and applying the system to bulk. This allowed controlled polymerisation of styrene to higher

molecular weights (~ 50000 g mol^{-1}) while maintaining a good agreement between theoretical and experimental molecular weights and achieving low dispersities.

The second half of the thesis focused on cationic polymers and in particular PDMAEA. This polymer has many desirable properties, in terms of a self-catalysed hydrolysis mechanism providing a release mechanism when applied to gene delivery applications. However this polymer is particularly challenging to synthesise, especially with copper mediated techniques. In Chapter 4, well-defined PDMAEA 4-arm and 8-arm stars were synthesised. Reactions were stopped at limited conversions (~40%) so to prevent star-star coupling, side reactions and termination events. This yielded star polymers with narrow molecular weight distributions. Importantly, a PDMAEA macroinitiator was isolated and purified, and subsequently utilised to make well-defined block copolymers. Issues with terminating the polymerisation and subsequently purifying the resultant material were overcome. Finally, the storage of these PDMAEA stars was also demonstrated, eliminating hydrolysis and preventing star-star coupling.

Finally in chapter 5, linear and star PDMAEA were successfully illustrated to hydrolyse in solution independent of environmental conditions. These polymers were able to bind and subsequently release dsRNA in solution, but a notable effect of the architecture was observed, with slower release of the star polymer than the analogous linear polymer. When applied to soil, star PDMAEA protected dsRNA illustrating a significantly greater stabilisation time of 3 weeks compared to naked dsRNA which degraded after 3 days. This work creates the basis for many new opportunities by using RNAi in agrochemical applications.

Publication List

Peer Review Articles

14. N. D. Dolinski, Z. A. Page, E. H. Discekici, I. Lee, D. Meis, G. R. Jones, **R. Whitfield**, X. Pan, B. G. McCarthy, S. Shanmugam, V. Kottisch, B. P. Fors, C. Boyer, G. M. Miyake, K. Matyjaszewski, D. M. Haddleton, J. Read de Alaniz, A. Anastasaki, C. J. Hawker, What happens in the dark? Assessing the temporal control of state-of-the-art photo-mediated controlled radical polymerizations, **J. Polym. Sci. A. Polym. Chem**., Just Accepted

13. E. Liarou†, **R. Whitfield**†, A. Anastasaki, N. G Engelis, G. R. Jones, K. Velonia, D. M Haddleton, Copper Mediated Polymerisation Without External Deoxygenation or Oxygen Scavengers, **Angewandte Chemie**, 2018, 57, 8998-9002

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12. **R. Whitfield**, A. Anastasaki, G. R. Jones, D. M. Haddleton, Cu(0)-RDRP of Styrene: Balancing initiator efficiency and dispersity, **Polym. Chem**., 2018, **9**, 4395-4403

11. A. Cook, R. Peltier, M. Hartlieb, **R. Whitfield**, G. Moriceau, J. A. Burns, D. M. Haddleton, Sebastien Perrier, Cationic and Hydrolysable Branched Polymers by RAFT for Complexation and Controlled Release of dsRNA, **Polym. Chem**., 2018, 7, 909-915

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Book Chapter

1. One-Pot Sequence-Controlled (SC) Multiblock Copolymers via Copper-Mediated Polymerisation, A. Anastasaki, **R. Whitfield**, V. Nikolaou, N. P Truong, G. R Jones, N. G Engelis, E. Liarou, M. R Whittaker, D. M Haddleton, **Sequence-Controlled Polymers**, John Wiley & Sons, 2018 (Invited)